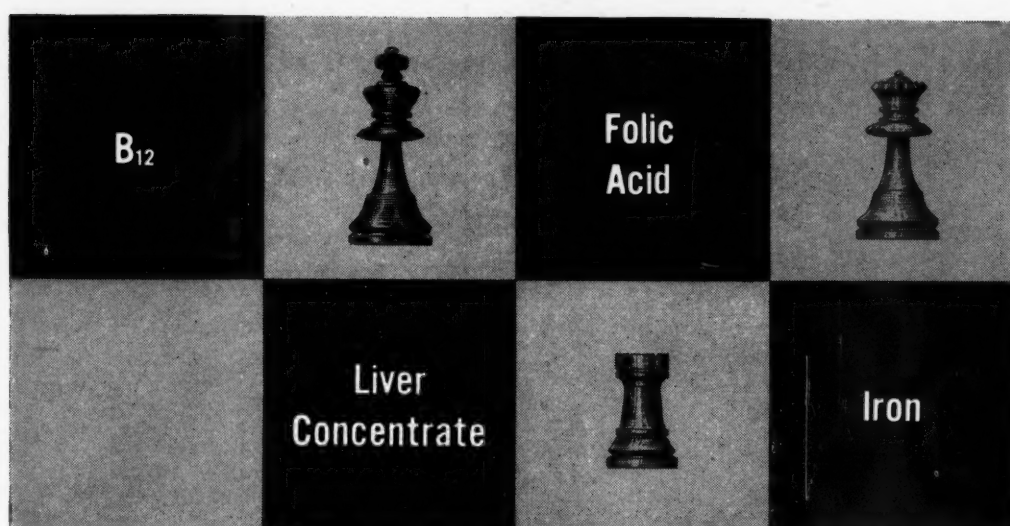


The
American Journal
of Medicine



Symposium on
The Adrenal Glands

May 1951



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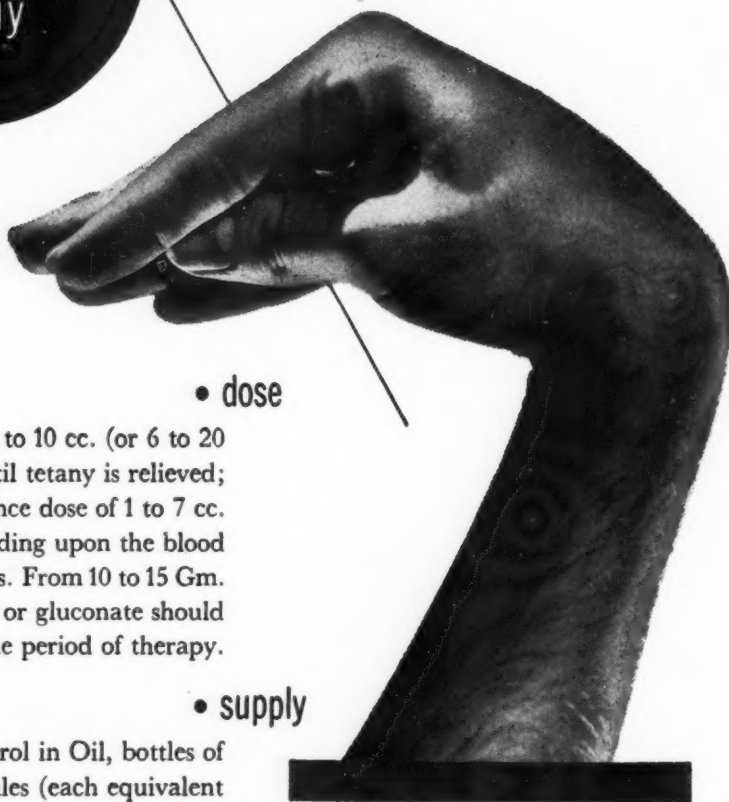
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Niacinamide	10 mg.
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C O N T E N T S

The American Journal of Medicine

Vol. X May, 1951 No. 5

SYMPOSIUM ON THE ADRENAL GLANDS

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Although much has been written about the adrenal glands, there seems to be need for a composite treatment of the subject, particularly of its more recent aspects, by first hand investigators in the field who write with authority, insight and considered judgment. With the advice and help of Dr. Robert F. Loeb, the Editor undertook to assemble such a Symposium. As will be evident to the reader, the invited participants have spared no effort in collaborating to the fullest extent. The result is a scholarly analysis of present views concerning the chemical, physiologic and clinical aspects of adrenal function. The reader will find this Symposium invaluable for orientation in this field.

Contents continued on page 5

Every diabetic survey emphasizes the startling percentage of unknown diabetics in our population—and increasing longevity is constantly adding to this total.

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The American Journal of Medicine

Vol. X May, 1951 No. 5

*Contents continued from page 3**Seminars on Pulmonary Physiology*

Pulmonary Fibrosis and Respiratory Function

GEORGE W. WRIGHT AND GILES F. FILLEY 642

The authors carefully analyze the factors in pulmonary fibrosis which may alter pulmonary function. Citing the clinical and laboratory observations made in nine illustrative cases representing different causes and stages of pulmonary fibrosis, the authors consider the mechanisms involved insofar as these are revealed by available measures of pulmonary function. The relations between fibrosis and emphysema and between histologic and physiologic criteria of emphysema are discussed informatively.

Case Report

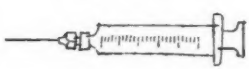


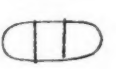
- Coexisting Acromegaly and Cushing's Syndrome. Discussion of Hormone Production by the Pituitary Acidophilic Cell ROBERT V. McCORMICK,
CHARLES E. REED, RAYMOND H. MURRAY AND BRONSON S. RAY 662

An interesting case report, with operative and necropsy findings, of coexisting acromegaly and Cushing's syndrome associated with pituitary acidophilic adenoma and adrenal hyperplasia and adenomas. The authors speculate on mechanisms.

For the Common Anemias...

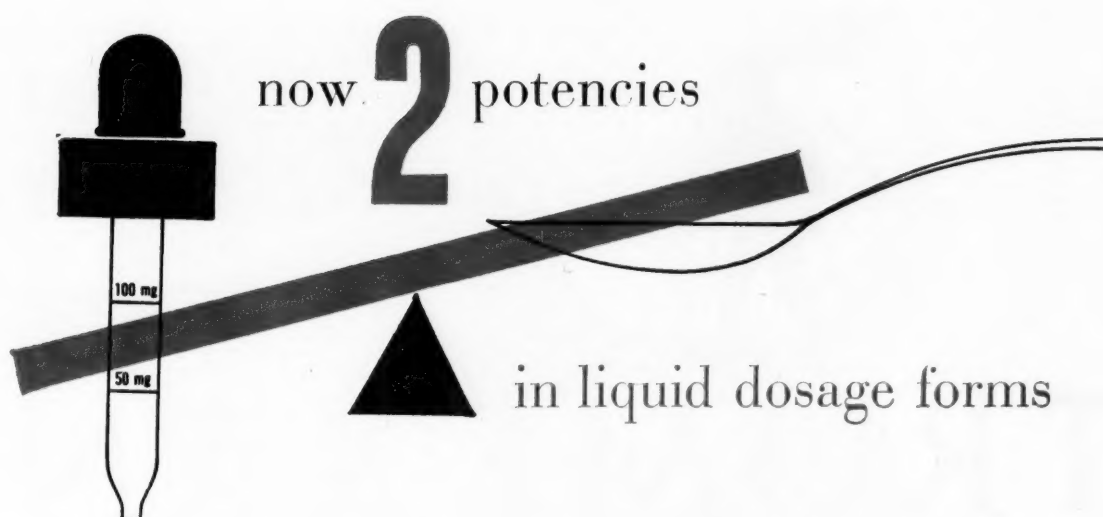


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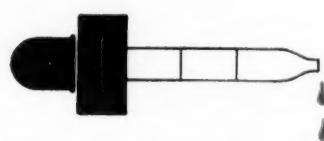


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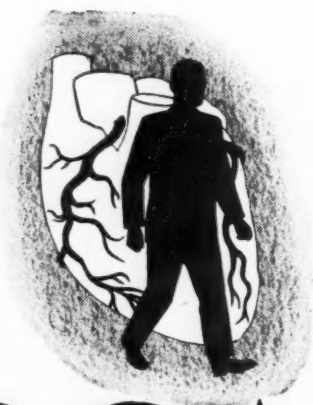
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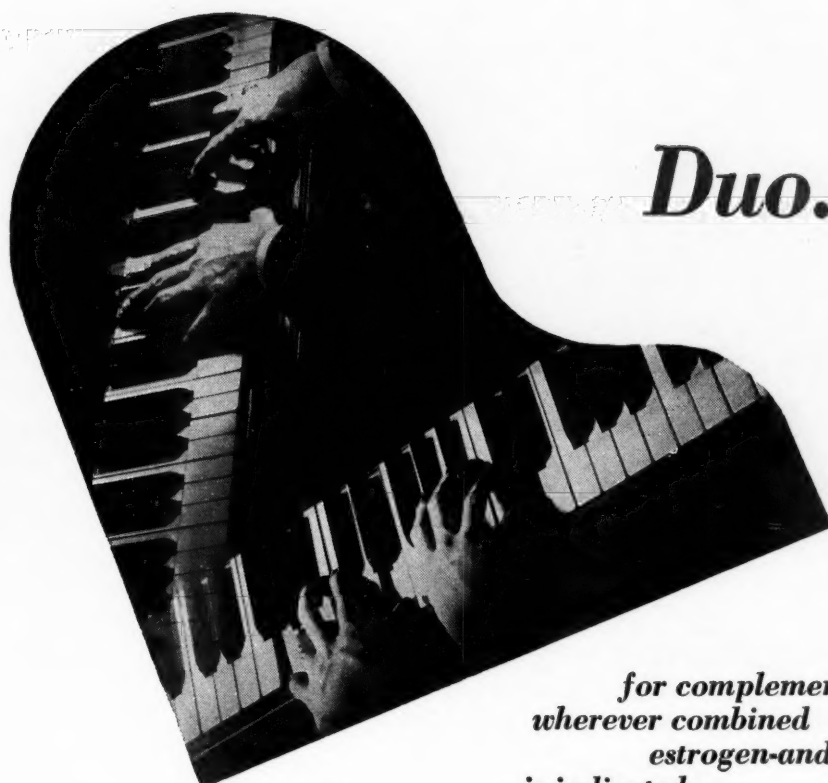
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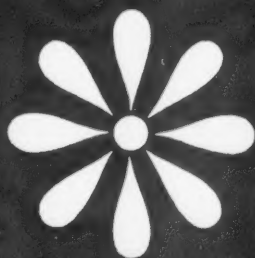
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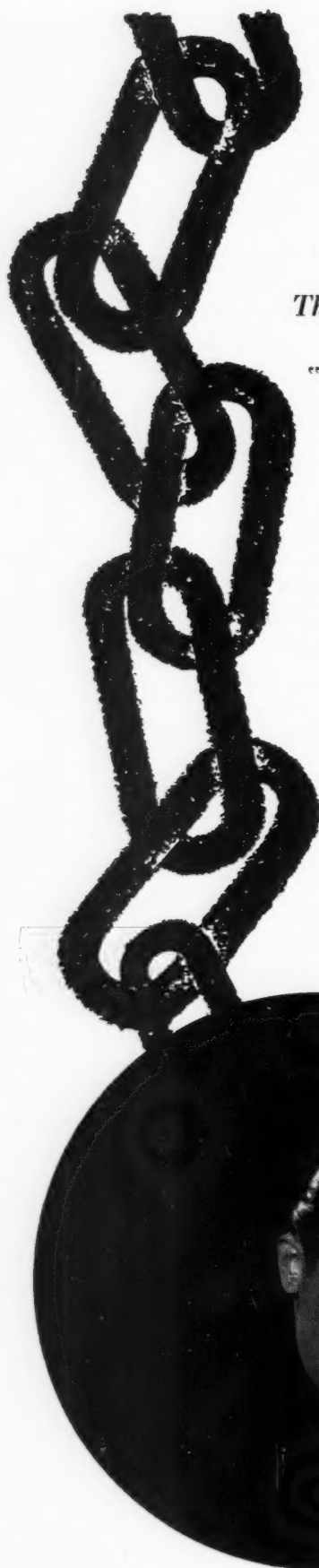
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Washburne, A.C.: Ann. Int. Med. 32:265, 1950.

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1. Kantor, J. L., and Kasich, A. M.: Handbook of Digestive Diseases, ed. 2, St. Louis, C. V. Mosby Co., 1949, p. 66.

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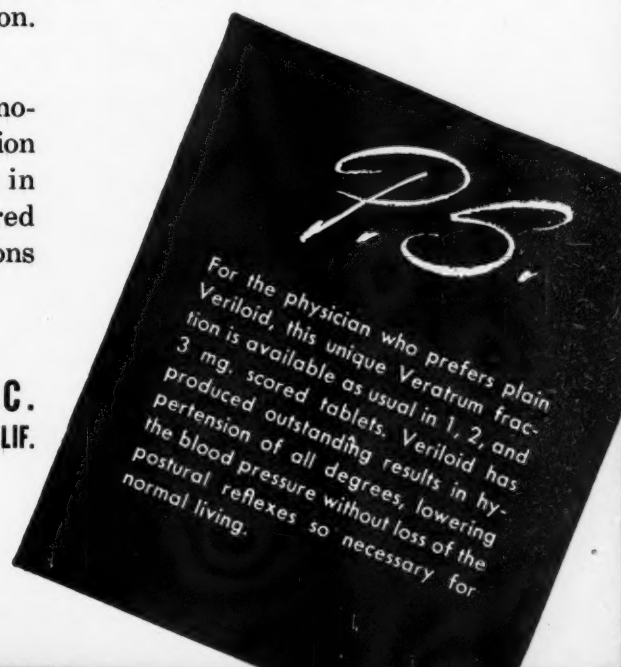
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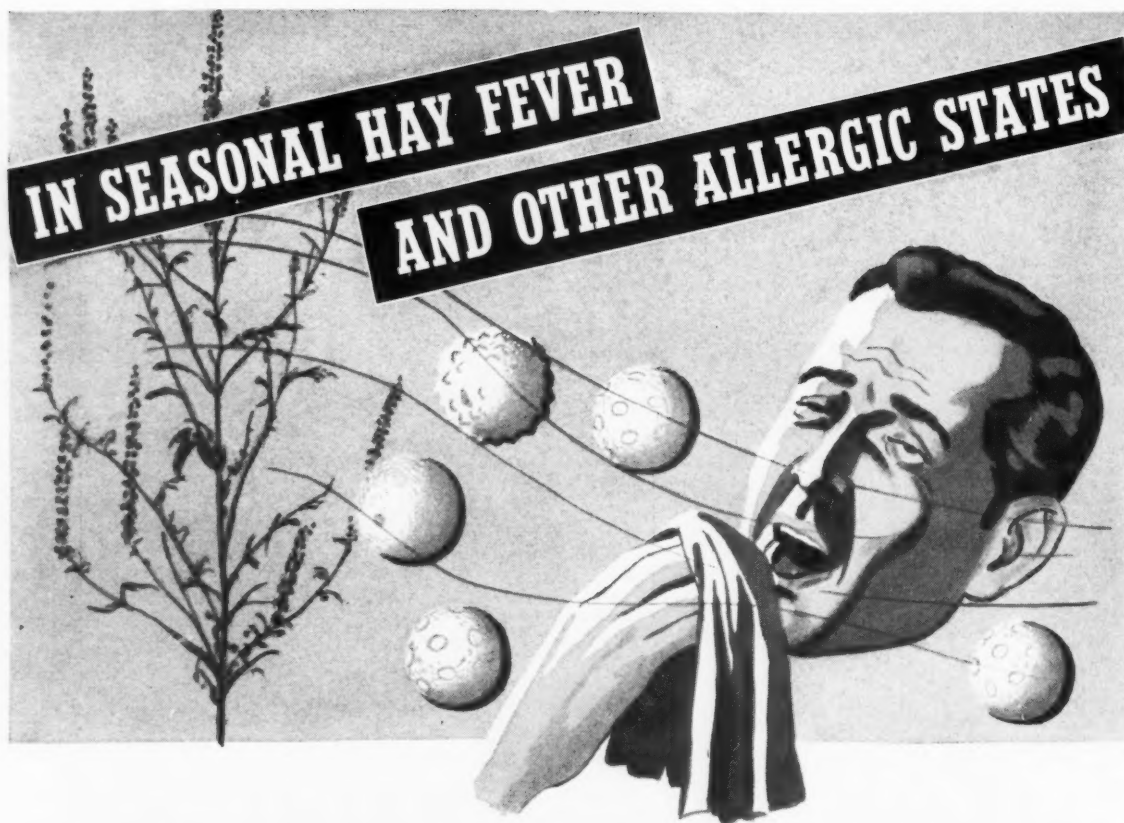


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*Reference: MacBryde, C. M., et. al., A New Synthetic Estrogen, J.A.M.A., 123: 261: 264-16-3) 41.

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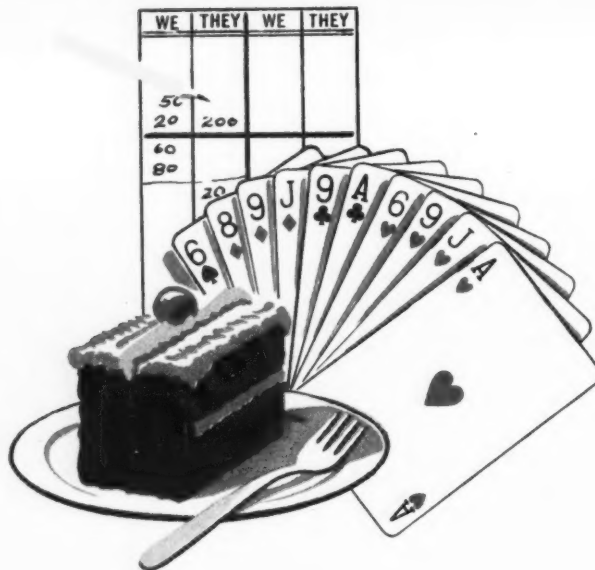
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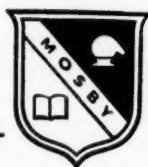
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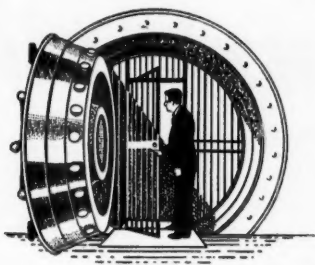
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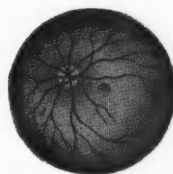
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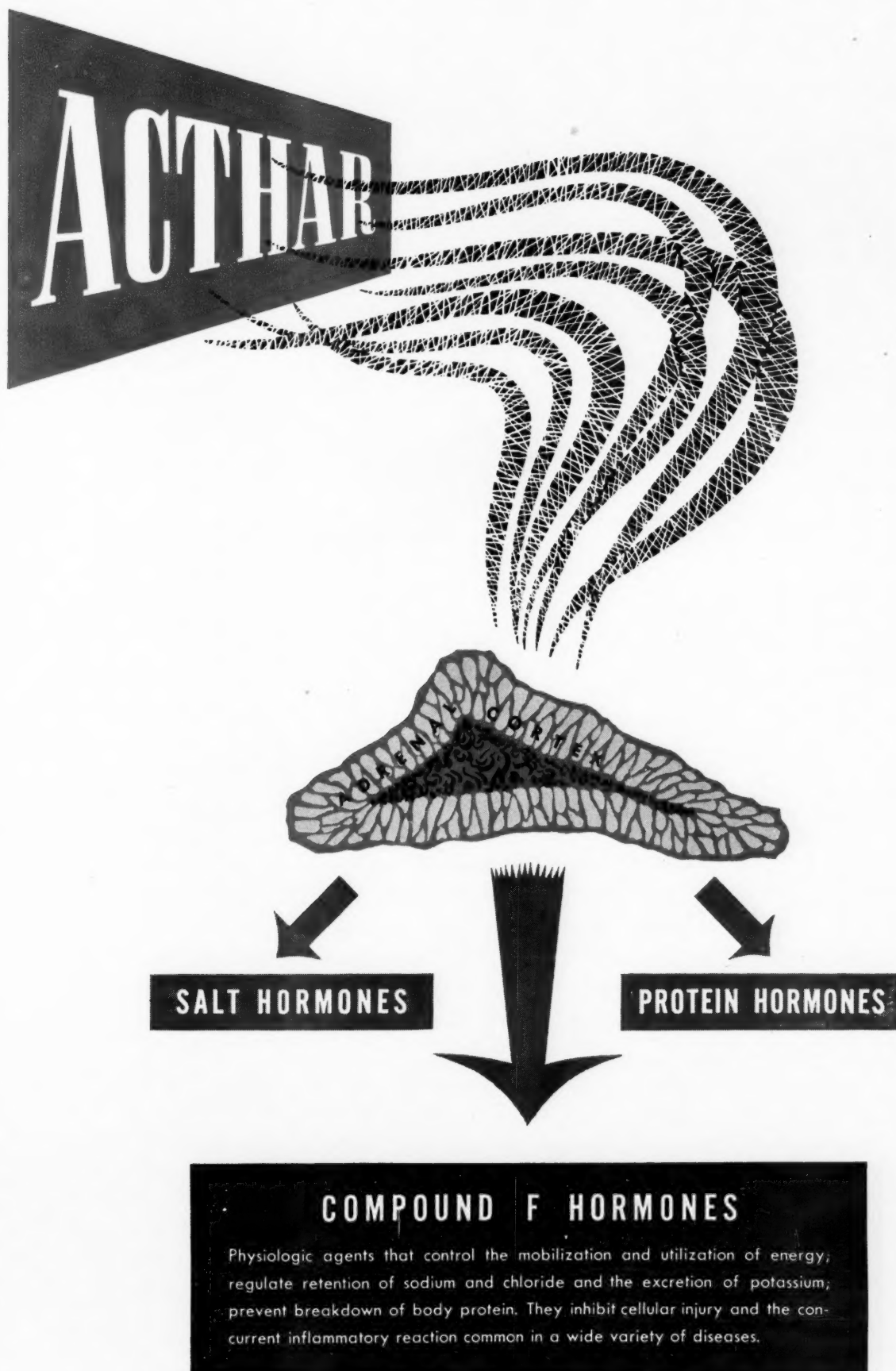
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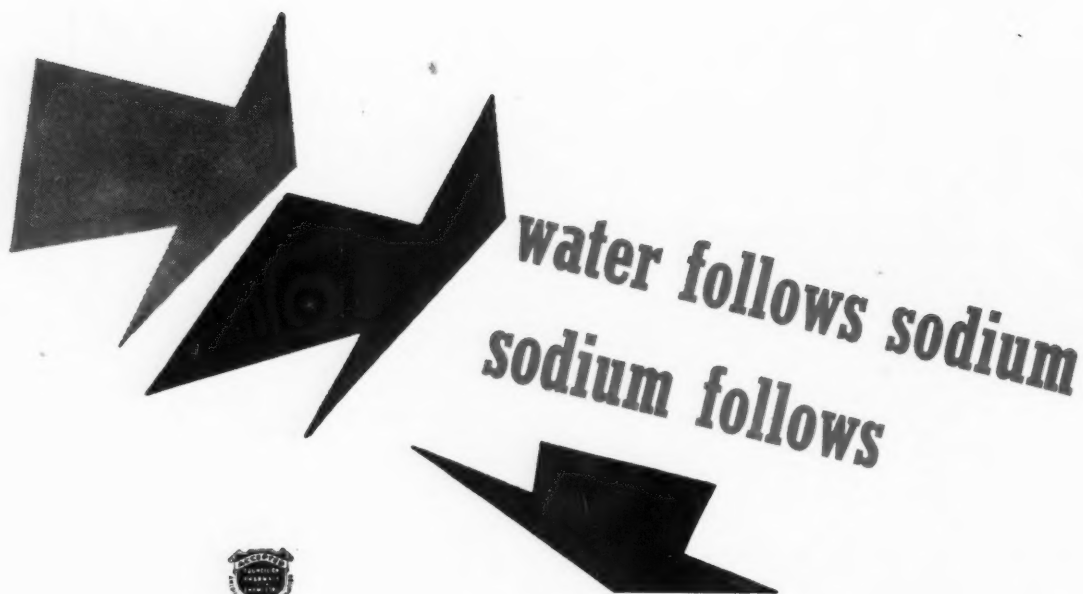
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2) Smith, R. T.: Journal-Lancet 70: 192, 1950

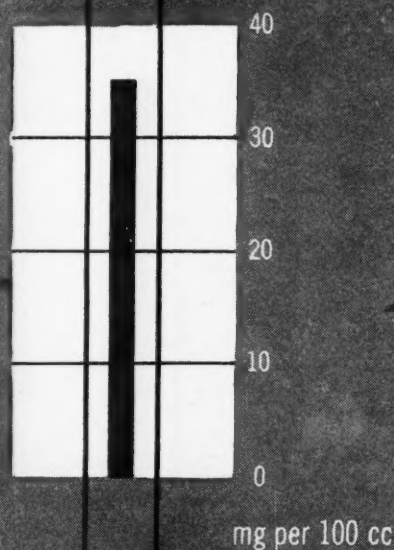
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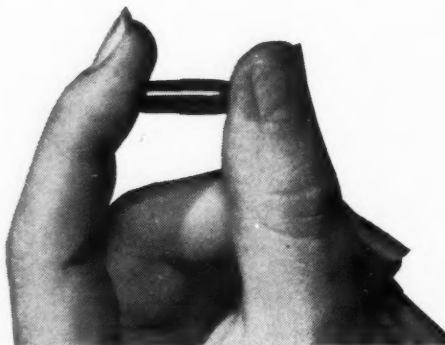
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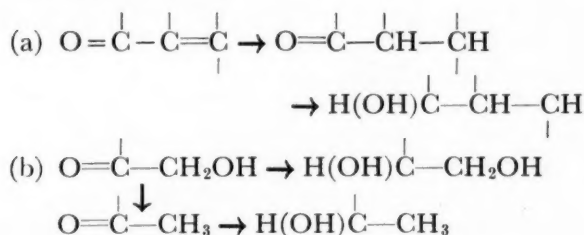
Symposium on the Adrenal Glands

The Chemistry of Adrenal Steroids*

R. P. JACOBSEN, PH.D. and G. PINCUS, SC.D.

Shrewsbury, Massachusetts

THE brilliant chemical investigations¹ of adrenal steroids begun in 1935 by Wintersteiner and Pfiffner, by Kendall and by Reichstein have earned for the latter two investigators a share in the 1950 Nobel Prize in Medicine. Twenty-eight crystalline substances have been isolated in these studies and the elucidation of their constitution has been accomplished through a variety of inter-conversions and partial syntheses from more readily available steroids. Of these twenty-eight compounds only six have been found to be capable of maintaining life in adrenalectomized animals. These hormones (Fig. 1) are accompanied in the gland concentrates by a number of inactive pregnane derivatives in which either one or both the unsaturated carbonyl (a) and ketol (b) groupings typical of the active hormones are reduced:



Since the nature of this short account precludes any mention of hundreds of chemical investigations of adrenal steroids reported during the past fifteen years, only a brief outline of the chemistry of the six active compounds pictured above will be presented here.

All of these substances are sensitive to alkali (ketol and unsaturated carbonyl groups) while those possessing a hydroxyl at C₁₁ or C₁₇ are sensitive to acids. The ketol group renders these compounds capable of reducing silver diamine solution and the two hormones containing a hydroxyl group at C₁₁ show an intense green fluorescence when mixed in trace amounts with concentrated sulfuric acid.

Desoxycorticosterone was prepared² by partial synthesis from 3-acetoxy-5-etiocholenic acid prior to its isolation³ from adrenal glands. The synthesis procedure (Fig. 2) involves the conversion of the etio acid (I) to the chloride (II) which is treated with diazomethane. The resulting diazoketone (III) after hydrolysis of the 3-acetoxy group is then oxidized to 21-diazo-progesterone (IV) which on treatment with acetic acid provides desoxycorticosterone acetate. The free ketol may be obtained by gentle hydrolysis of the acetate with acid or preferably⁴ with potassium bicarbonate solution.

Corticosterone was the first active hormone to be isolated⁵ from glandular extracts. The ketol structure (Fig. 3) was established^{5b} by oxidative cleavage with periodic acid, with the formation of formaldehyde and a carboxylic acid (I) which on further oxidation provided the diketone acid II. The evidence obtained in these transformations gave the first indication of the presence in the molecule of the inert oxygen function later shown to be at C₁₁. In another significant series of reactions⁶ the position of the ketol group at C₁₇ and the oxygen at C₃ were established. Corticosterone was converted to the *p*-toluenesulfonate (III) and the crude ester was treated with sodium iodide. The resulting iodo compound (IV) was then reduced to 11 β -hydroxyprogesterone. This derivative could be readily dehydrated by acid, providing V which was converted to allopregnane-3,20-dione as indicated. The placement of the unreactive hydroxyl group of corticosterone was established by the mild oxidation^{5a} of its 21-acetate to dehydrocorticosterone acetate which has been prepared by a variety of synthesis procedures.

Dehydrocorticosterone was isolated first by Kendall^{5b} and later by Reichstein⁷ and by Kuizenga and Cartland.⁸ The Mayo Clinic investigators showed that it could be converted by chromic acid oxidation to the same diketone acid (Fig. 3, II) obtained from corticosterone.

* From the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and the Tufts College Medical School, Boston, Mass.

Since no readily available steroid containing an 11-oxygen function has yet been discovered, the starting material for the partial synthesis of dehydrocorticosterone is a 12-oxygenated steroid such as desoxycholic acid. The acid or one of its side chain degradation products must first be

benzoate (I) which on pyrolysis gives the 11,12-unsaturated compound II. This may be treated with hypobromous acid forming a mixture containing the bromohydrin (III) which after oxidation and debromination yields the 11-keto compound XI.

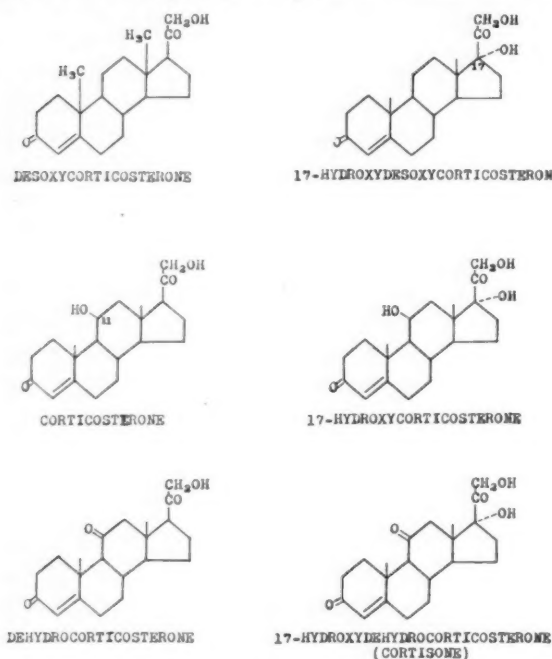


FIG. 1.

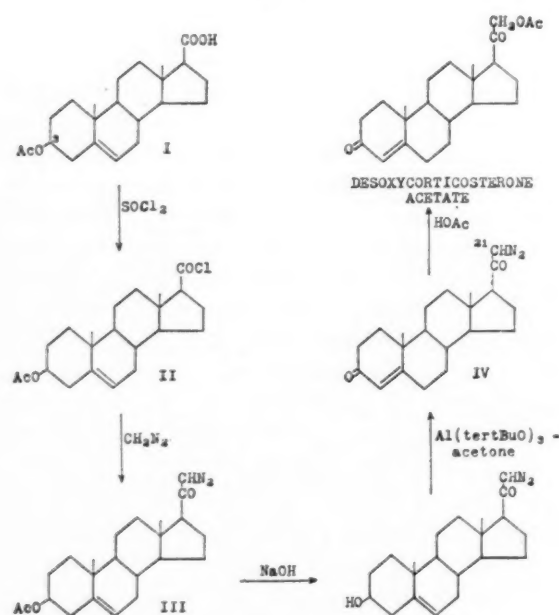


FIG. 2.

transformed to an 11-keto compound as illustrated by the partial formulas of Figure 4. According to method (a) a suitable derivative of desoxycholic acid is converted⁸ to the 12-

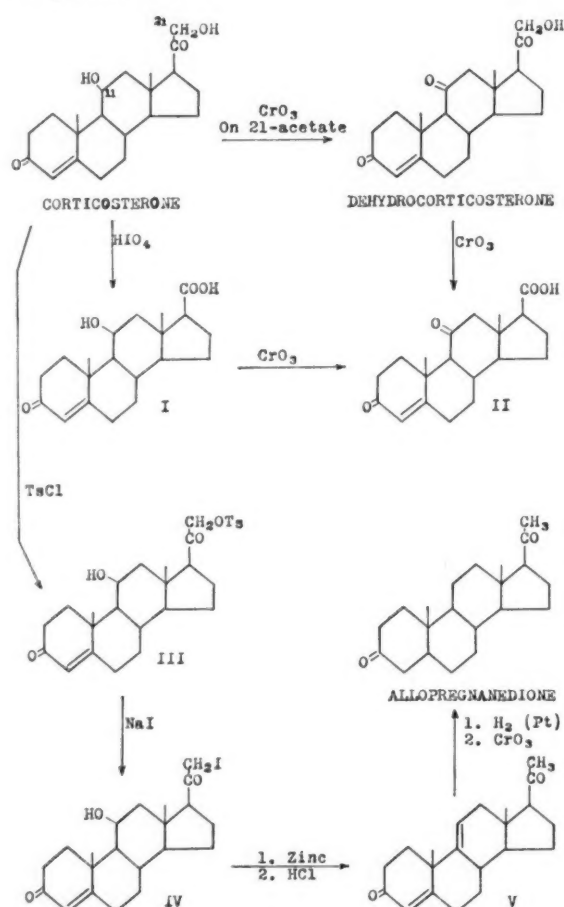


FIG. 3.

In a second method⁹ (b) a 12-keto bile acid derivative (V) is oxidized with selenium dioxide¹⁰ followed by catalytic reduction, yielding the allylic alcohol VI.¹¹ In this compound the hydroxyl group is easily replaced by halogen and the latter readily eliminated, providing an 11,12-unsaturated compound (VII) containing a 3,9-oxide bridge. Through bromination of VII at a low temperature a mixture of isomeric dibromides is formed which by treatment with silver oxide gives a bromohydrin. Oxidation of the latter yields the 3,9-oxide (VIII) of a 12-bromoketone corresponding to IV. In the subsequent side chain degradation of VIII the oxide ring is opened and the bromine atom replaced by hydrogen.

In a third method¹² (c) for the introduction of

oxygen at C₁₁ the mixture of epimeric bromoketones (IX) formed in the bromination¹³ of V is treated with alkali^{13a,14} yielding a 12-hydroxy-11-keto compound (X). The 12-hydroxyl group is then replaced as indicated.

In order to convert an 11-ketonic desoxycholic

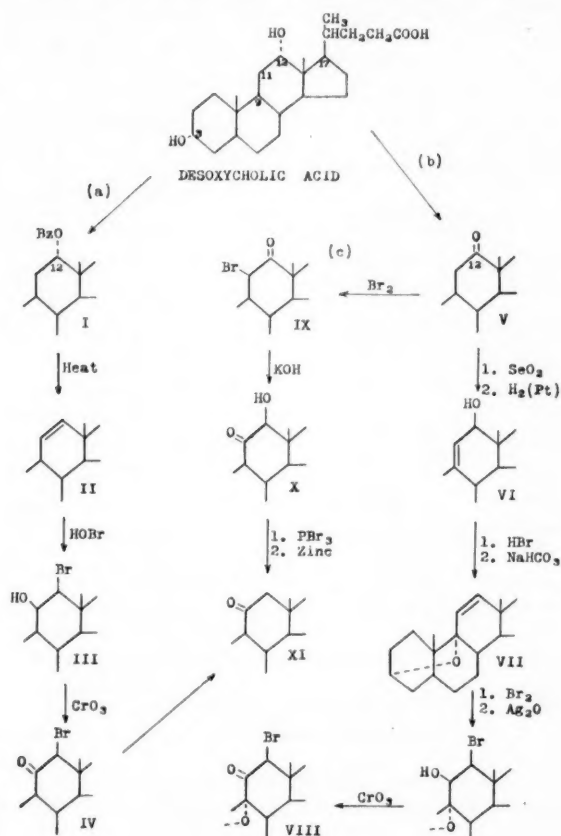


FIG. 4.

acid derivative to an active adrenal steroid it is necessary to replace the bile acid type side chain with the ketol group. One of the processes for doing this was employed in the synthesis¹⁵ of dehydrocorticosterone. (Fig. 5.) An ester of the 11-keto acid is allowed to react with phenylmagnesium bromide and the resulting diphenylcarbinol is dehydrated and re-acetylated to form I. This on bromination with N-bromosuccinimide followed by debromination with pyridine yields the diene II. At this stage the hydroxyl group at C₃ may be oxidized and the diketone (III) thus obtained is again treated with N-bromosuccinimide. The bromo compound is this time allowed to react with potassium acetate which replaces the bromine atom with an acetoxyl group, forming IV. Mild chromic acid oxidation of this compound results in side chain cleavage with production of the

triketone V, which is converted to dehydrocorticosterone acetate by formation of the 4,5-double bond.

17-Hydroxydesoxycorticosterone was isolated by Reichstein.⁷ The substance closely resembles 17-hydroxydehydrocorticosterone (cortisone) in

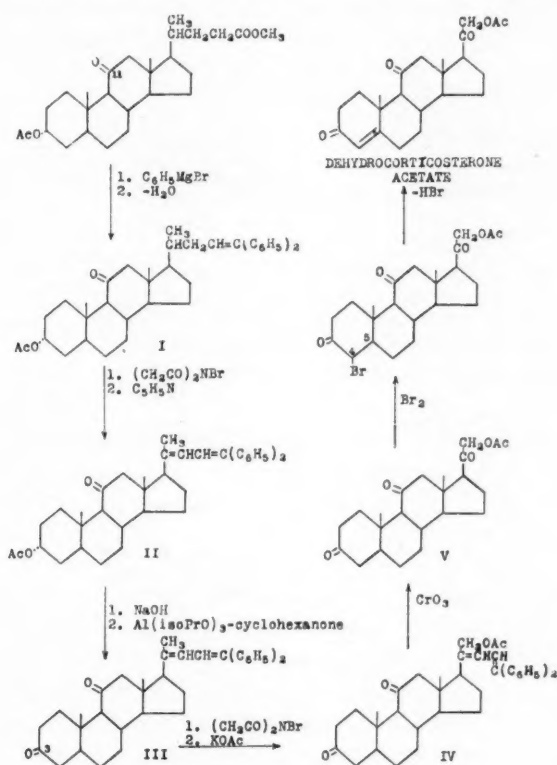


FIG. 5.

its melting behavior but the two hormones may be differentiated by the sulfuric acid test, the desoxy-hormone producing a characteristic red color. The constitution of 17-hydroxydesoxycorticosterone was suggested by the isolation of 4-androstene-3,17-dione as a product of chromic acid oxidation and the structure was established¹⁶ by synthesis from dehydroepiandrosterone. Of the several methods which have been devised for the preparation of 17 α -hydroxy steroids, the one recently developed by Julian and his collaborators¹⁷ for the synthesis of 17-hydroxydesoxycorticosterone is shown in Figure 6. Starting material for this synthesis is pregnenolone which after conversion to the diene acetate (I) by a bromination-debromination process¹⁸ is transformed to the 16,17-oxide (II) through treatment with alkaline hydrogen peroxide. The oxide is allowed to react with bromine and hydrogen bromide in four stages and the resulting crude tetrabromide (III) is debrominated

in situ with sodium iodide and potassium acetate providing IV. Generation of the unsaturated carbonyl group in IV followed by re-opening of the oxide ring with hydrogen bromide provides the bromohydrin V which yields the hormone acetate on reduction with Raney nickel.

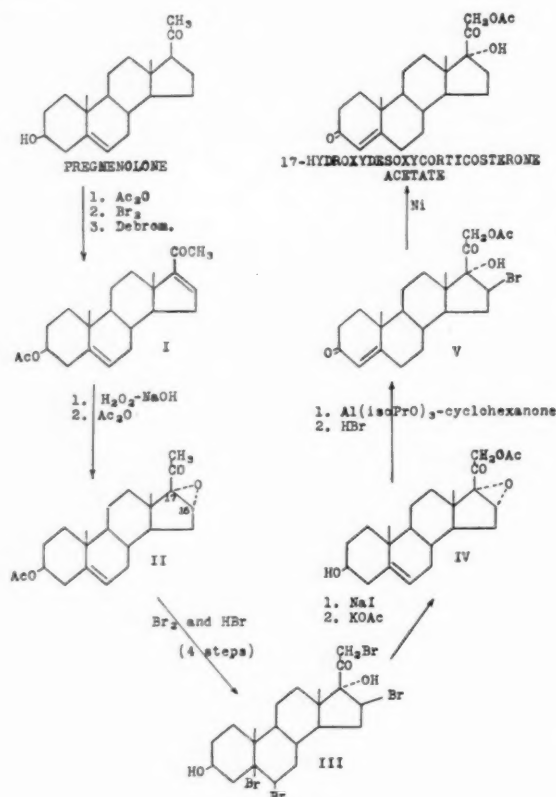


FIG. 6.

17-Hydroxycorticosterone was isolated^{3,19} by Reichstein, by Kendall, and by Kuizenga and Cartland. In oxidative degradation reactions,^{19b,20} similar to those described for corticosterone in Figure 3, the 17-hydroxy hormone was converted to 4-androstene-3,11,17-trione (adrenosterone). The alcoholic nature of the C₁₁ oxygen function was demonstrated²¹ by the mild chromic acid oxidation of 17-hydroxycorticosterone 21-acetate to 17-hydroxydehydrocorticosterone (cortisone) acetate.

17-Hydroxydehydrocorticosterone (Cortisone) has been isolated²² from glandular extracts in four laboratories. The important discovery²³ by investigators at the Mayo Clinic of the chemotherapeutic value of cortisone in the treatment of rheumatoid diseases has provided great impetus to studies of the synthesis of this hormone from readily available steroids. One of

the synthesis procedures²⁴ (Fig. 7) has been adapted for the manufacture of cortisone acetate. Starting material for this synthesis may be conveniently prepared by brominating the diene acetate (Fig. 5, II) mentioned previously with N-bromosuccinimide and subjecting the product to acetoxylation, forming I. The oxida-

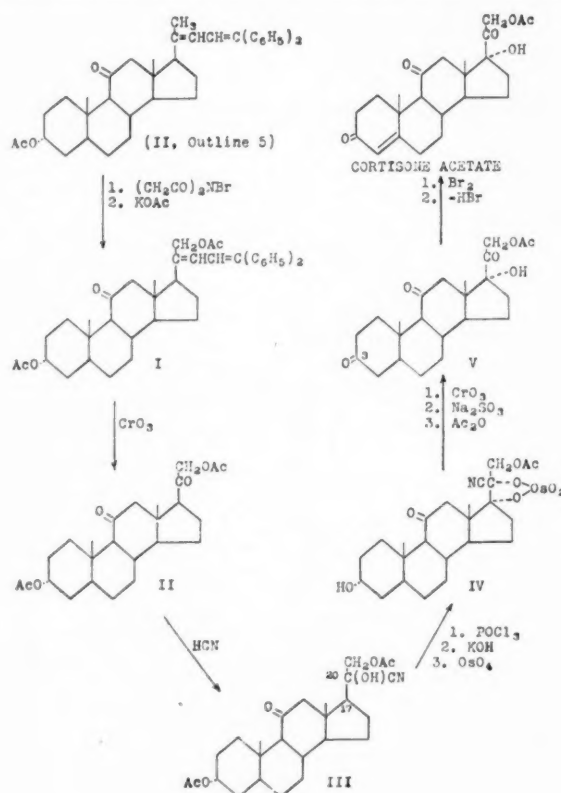


FIG. 7.

tive cleavage of the side chain of this compound then provides the starting material II which is first converted to the cyanohydrin III. Dehydration of this substance affords an intermediate 17,20-unsaturated compound to which osmium tetroxide is added. The osmic ester (IV) proved to be suitable for oxidation to the 3-keto compound which after reductive hydrolysis and re-acetylation provides V. Cortisone acetate is satisfactorily obtained from V by bromination-debromination according to the method of Mattox and Kendall.²⁵

THE BIOGENESIS OF ADRENAL STEROIDS

The isolation of a variety of steroids from adrenal tissue has raised several questions. Are the steroids that have been isolated in fact adrenal secretory products, or may some or most of them be artifacts arising either as the

result of infection and/or autolysis of the extirpated gland or created by the type of extraction and isolation procedures employed? What are the precursors of the corticosteroids and how is their biosynthesis promoted? Complete answers to these questions are not available but recent evidence based on two experimental procedures

TABLE 1*

Experiment	1	2	3	4
α -Ketols†				
Unknowns I-V	450	600	550	700
17-Hydroxycorticosterone	1000	1100	1700	1100
Cortisone	120	60‡	50	200‡
Unknown VI	120		110	
Unknowns VII-IX	150		800	250
Corticosterone	1200	1300	1800	1100
Unknown X	450§	400§	330	300
11-Dehydrocorticosterone			330	250
11-Desoxycorticosterone	120	140		

* Micrograms (per 2 L.) of various α -ketols in the perfused blood after the perfusion of ACTH (6 mg. per L.) at a flow of 1 L. per hour. The order of the compounds is from the most polar (unknowns I to V) to the least polar (11-desoxycorticosterone).

† Unknown III may be allopregnanetetrol-3 β , 11, 17, 21 one-20.

Unknown X may be pregnanediol-3 β , 21, one-20.

Unknown VI may be allopregnanetriol-3 β , 17, 21, one-20.

‡ Total of cortisone plus unknown VI.

§ Total of unknown X plus 11-dehydrocorticosterone.

.... No determination made.

suggests probable modes of origin. The two procedures involve the analysis of adrenal venous blood taken from anesthetized animals and similar analysis of blood perfused through the isolated adrenal *in vitro*. Identification of the corticosteroids in these bloods has been accomplished by isolation of specific steroids or the application of paper chromatography with recently developed methods for corticosteroid separation.^{26,27} Corticosterone and 17-hydroxycorticosterone have been identified as components of adrenal vein blood of the dog following ACTH administration,²⁸ and most recently 11-hydroxyandrostenedione has been tentatively identified.²⁹

An intensive investigation of the products of beef adrenal gland perfusion has led to the identification of fifteen α -ketols occurring in rather constant pattern after ACTH administration to the isolated gland. In Table 1 are

presented the data on corticosteroid output in four experiments in which ACTH-containing blood was perfused once through a single gland in each case.³⁰ These data demonstrate: (1) that 17-hydroxycorticosterone and corticosterone are regularly present in largest amount, (2) that 11-dehydrocorticosterone, 11-desoxycorticosterone

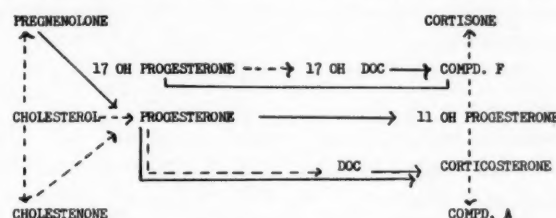


FIG. 8. A tentative scheme of corticosteroidogenesis wherein cholesterol is assumed to be the primary steroid precursor. The solid lines represent reactions which have been demonstrated; the dotted lines represent possible reactions which have not, as yet, been demonstrated.

and cortisone are present also but in lesser amount and in descending concentration, (3) that considerable amounts of highly polar components (unknowns I to V) occur regularly, (4) that less polar compounds are also regularly present and (5) that among the unknown compounds tentatively identified are obvious reduction products of the hormonally active corticosteroids. Glands perfused in the absence of ACTH contain rather small amounts of each of these components, and the concentration of individual components following ACTH addition to the medium increases four- to tenfold^{30,31} in one hour's perfusion. The adrenocorticotrophic hormone of the pituitary acting directly on adrenal tissue thus stimulates the production of a variety of corticosteroids.

Clues to the mechanism of action of ACTH come from perfusion studies with various steroids added to the medium.^{31,32a,b,c} These studies demonstrate: (1) that 11-desoxycorticosterone and 11-desoxy-17-hydroxycorticosterone are converted by the adrenal to corticosterone and 17-hydroxycorticosterone, respectively, (2) that no further conversion of the 11-hydroxylated products occurs and (3) that Δ^5 pregnenolone and progesterone perfusion leads to the production of a number of more highly hydroxylated products, the principal products being again corticosterone and 17-OH corticosterone. In Figure 8 a scheme of steroidogenesis is presented derived from the data of these studies, suggesting a dual pathway to the two major end-products, 17-hydroxycorticosterone and corticosterone;

this scheme suggests that cortisone and 11-dehydrocorticosterone are metabolites of 17-hydroxycorticosterone and corticosterone, respectively. Since ACTH added to the perfusion medium does not appear to enhance the hydroxylation of the precursors studied, the authors suggest³¹ that it may act to assist the breakdown of cholesterol to the 21-carbon precursors.

Cholesterol is indicated as a probable parent compound of the adrenocorticosteroids on the basis of indirect and direct evidence: (1) Its concentration in the gland is significantly lowered following ACTH administration *in vivo*^{33a,b} and (2) following the perfusion of C-14 labelled cholesterol through the isolated adrenal C-14 containing corticosteroid is obtained.³⁴ The evidence that adrenal cholesterol may be synthesized directly from acetate has been demonstrated *in vitro* with adrenal slices incubated with radioacetate,³⁵ and perfusion of the latter through the isolated beef adrenal results in the production of both radiocholesterol and radiocorticosteroid.^{30,34}

Most of the foregoing evidence deals with the genesis of steroid α -ketols. The isolation of estrogen and androgen from adrenal tissue¹ suggests the synthesis of these types of compounds by adrenal tissue. Direct evidence is still lacking, however, and the possibility that they may represent secondary metabolites of typical corticosteroids is not excluded. An interesting enzymatic mechanism for steroidogenesis undoubtedly exists in the adrenal and already evidence for an isolable 11-hydroxylating enzyme system has been reported.^{36a,b,c}

THE METABOLISM OF ADRENAL STEROIDS

Our principal information concerning the metabolic fate of adrenocorticosteroids comes from studies of urinary steroids, chiefly in man. The urinary steroids reflecting adrenal secretory function are the 17-ketosteroids and the corticosteroids. The former are compounds not directly derived from the adrenal itself since none of them have been isolated from adrenal tissue. In normal human urine the 17-ketosteroids regularly found are: androsterone, etiocholanolone, epiandrosterone, dehydroepiandrosterone, 11-ketoetiocholanolone and 11-hydroxyandrosterone. In actual practice the quantitative extraction of the 17-ketosteroids requires hydrolysis of the urine since these substances are excreted as esters; as a result of the hydrolysis

certain artefact substances appear (e.g., androstenone-17, androstadienone-17) which derive from the parent compounds listed before. In the male a certain proportion of some of the 17-ketosteroids (e.g., androsterone, etiocholanolone) derive from testis precursors but they are in largest part adrenal steroid metabolites (in females practically completely so). The evidence for their derivation from adrenal precursors depends on their great diminution in the urine of patients with Addison's disease and following adrenalectomy, and their increase in hyperadrenal states (Cushing's syndrome, adrenogenital syndrome) and following ACTH administration. This evidence has been extensively reviewed by a number of authors (e.g., Heard,¹ Fieser and Fieser,¹ and others).^{37a,b,c}

Certain non-ketonic steroids found in human urine appear also to reflect adrenocortical activity. Again, a mixture of substances appears to be involved, the exact nature of the components still being undefined although pregnanediol, etiocholanediol and androstanediol have at times been identified as non-ketonic constituents. Methods for the measurement of non-ketonic steroids as a group of substances have been discussed by Engle.³⁸

The chemical nature of the various urinary corticosteroids remains to be elucidated. It has been established that cortisone and 17-hydroxycorticosterone are components of the corticosteroid mixture^{39a,b} but the presence of other compounds biologically active and inactive is clearly indicated. Schneider^{38a} has obtained four additional crystalline compounds of which one is clearly a reduction product of cortisone. Following ACTH administration to man 17-hydroxycorticosterone is the principal urinary corticosteroid found.^{38b} Methods for the quantitative extraction of these compounds are still to be perfected. Apparently, chemical hydrolytic methods employed to date are more or less destructive of these substances and methods of enzymatic hydrolysis are being investigated. Again, the corticosteroids excreted into the urine vary with the adrenal state of the individual, much as do the 17-ketosteroids, but there is no regular correlation between the excretion of the two types of compounds⁴⁰ and in certain pathologic states the output of one may be abnormal while that of the other is normal.^{1,37b}

Studies of the metabolic fate of adrenocorticosteroids have until very recently been limited by the scarcity of most of the corticosteroids.

Pregnanediol-3 α , 20 α has been isolated from the urine after 11-desoxycorticosterone administration⁴¹ but the recovered pregnanediol represents only a small fraction of the administered desoxycorticosterone. Studies with side-chain labelled (with C-14) desoxycorticosterone in animals suggest that the α -ketol side chain may be oxidized *in vivo* to CO₂ and H₂O.⁴² The chief urinary metabolite of 11-dehydrocorticosterone administered to patients with Addison's disease proved to be 11-ketopregnanediol, again representing only a small fraction of the steroid administered.⁴³

Following cortisone administration to Addisonian patients an increase in 17-ketosteroid, non-ketonic steroid and corticosteroid in the urine is observed but again the urinary steroid increase accounts for only a few per cent of the cortisone administered.^{38,43} In patients with intact adrenals a depression of 17-ketosteroid output accompanies increased corticosteroid excretion.^{44,45} This appears to be due to depression of the secretion of endogenous 17-ketosteroid precursors by cortisone.^{33b} With the widespread therapeutic use of adrenal cortex steroids more detailed excretion studies may be expected, and with the synthesis of isotopically-labelled corticosteroids⁴⁶ detailed turnover studies are in prospect.

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Regulation of the Secretory Activity of the Adrenal Cortex*

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THE adrenal cortex is capable of undergoing remarkably rapid and extensive fluctuations in secretory activity in response to the varying needs of the organism for cortical hormone. The maximum secretory capacity of the gland may be estimated to be at least equal to the enormous quantities of cortical hormone which are required by the adrenalectomized animal or the patient with Addison's disease to maintain normal resistance to severe stress. The rapidity of response of the gland is demonstrated by the fact that manifestations of accelerated activity—adrenal ascorbic acid depletion in animals, eosinopenia in man—are apparent within a few minutes after application of stress. The magnitude and the rapidity of change in rate of secretion of the cortical hormone are controlled by the adenohipophysis. The adenohipophysis interprets the needs of the organism for cortical hormone and directs the secretory activity of the adrenal cortex accordingly. The subject of regulation of the secretory activity of the adrenal cortex may be conveniently divided into two phases: (1) the regulatory control of the adenohipophysis over the adrenal cortex and (2) the factors which influence the rate of discharge of adrenocorticotrophin from the adenohipophysis.

PITUITARY REGULATION OF THE SECRETORY ACTIVITY OF THE ADRENAL CORTEX

The adrenal cortex of the hypophysectomized animal or of the patient with panhypopituitarism is atrophic and inert to stress. In agreement with the anatomic and chemical indices of adrenocortical activity are the results of physiologic studies which indicate that the hypophysectomized animal, like the adrenalectomized animal, lacks the ability to resist stressful conditions.

However, there can hardly be any doubt that

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a relatively small quantity of cortical hormone is released at a steady fixed rate in the absence of the adenohipophysis. This steady secretion of a small amount of cortical hormone may explain the ability of the hypophysectomized animal to survive without salt therapy. In addition, sodiumphoresis, secondary to an adrenocortical insufficiency caused by the lack of adrenocorticotrophic hormone (ACTH), may be mitigated by the loss of other pituitary factors which act to enhance sodium excretion. The adrenalectomized animal has no source of cortical hormone and quickly succumbs unless given sodium chloride therapy; perhaps the presence of an active adenohipophysis even hastens death.

Swann⁷⁴ and Greep and Deane^{14,22,23} are impressed by the failure of the glomerulosa zone of the cortex to atrophy after hypophysectomy and consider this zone to be independent of pituitary control and capable of autonomously secreting a "salt-active" hormone for the maintenance of electrolyte balance. Evidence has been reviewed⁶¹ which indicates that the hypophysectomized animal and the patient with panhypopituitarism are able to maintain sodium balance under normal dietary and metabolic conditions but are unable to adjust to situations of electrolyte stress. The thesis that a specialized secretory zone of the adrenal cortex can vary its rate of secretion in the absence of the adenohipophysis has no incontestible evidence to support it.

The adenohipophysis exerts its regulatory influence over the adrenal cortex through the mediation of ACTH. The chemical nature of this substance is not yet settled. A homogeneous protein was isolated from sheep⁴⁰ and hog⁶⁵ pituitary tissue which has a specific trophic action on the adrenal cortex and which is free

from other pituitary trophic activities. This protein, which was reported to have a molecular weight of 20,000, may be "pure" in a biologic sense only. Lesh et al.³⁹ and Payne et al.⁵⁰ have isolated what appear to be polypeptide mixtures which are 100 or more times as potent as the so-called "pure" protein of 20,000 molecular weight. If the ACTH activity of the "pure" protein resides in a moiety which is split off by the fractionation procedures of Lesh et al.³⁹ or of Payne et al.,⁵⁰ the molecular weight of this moiety must be approximately 200 (20,000 divided by 100), a remarkably low molecular weight. On the other hand, it is quite possible that ACTH is carried along as a "contaminant" by the "pure" protein of Sayers et al.⁶⁵ and of Li et al.⁴⁰ Since the preparations of Lesh et al.³⁹ and of Payne et al.⁵⁰ are very potent, the mass of ACTH need be very small in comparison to the main bulk of so-called "pure" protein; physical-chemical methods employed for the evaluation of the homogeneity of proteins would fail to detect such a small mass. It is of interest in this connection that bioassay can readily detect contamination with adrenocorticotrophic or posterior pituitary principle when physical-chemical methods fail. A few years ago the problem of the chemistry of ACTH was thought to be settled. Currently it is very much an open question. The fact that proteolytic enzymes inactivate the biologic activity of ACTH suggests that it is a peptide. However, the number and the nature of its component amino acids are still unknown.

No substance other than ACTH has been demonstrated to have a direct trophic action on the adrenal cortex. In particular, no gonadotrophin has been shown to stimulate the adrenal cortex in the absence of the pituitary, except in the special case of the mouse in which a gonadotrophin acts directly upon the X zone.³⁷ There is no evidence from chemical fractionation studies to support the notion of Selye⁷¹ that the pituitary elaborates a "glucocorticotrophin," a "mineralocorticotrophin," a "lipocorticotrophin" and a "testocorticotrophin."

In man purified ACTH induces all the metabolic changes which have been ascribed to the adrenal cortex. ACTH administration results in metabolic changes characteristic of those produced by the 11,17-oxysteroids (diabetes mellitus-like changes in carbohydrate metabolism,^{5,10,17,45,62} sodiumphoresis,^{17,62} lymphocytopenia and eosinopenia;^{17,28,62} by

desoxycorticosterone acetate (DCA)* (sodium retention;^{10,17,45,53,62} and by androgens (acne and hirsutism^{11,18,45}). The trophic increases the urinary excretion not only of corticoids but also of 17-ketosteroids.^{5,44,62,77,79} It would appear that a single trophic, ACTH, can account for the numerous metabolic actions which have been associated with adrenocortical activity.

Selye,^{68,69,71} in an attempt to explain the variety of metabolic patterns which the organism may exhibit under different environmental conditions, has postulated the secretion of a "glucocorticoid," a "mineralocorticoid," a "lipocorticoid" and a "testocorticoid." The concept implies that the secretion of the adrenal cortex may vary in composition according to the requirements of the organism. Important as the adrenal cortex is in the regulation of the metabolic pattern of the organism, the multisteroid concept places an undue burden upon the gland; many other organs play an equally significant role in the adjustments of the milieu intérieur. The diversity of patterns of metabolic change which may occur in the organism is more likely a result of the possible varieties of interactions between the numerous organs of homeostasis on the one hand and the varieties of stresses on the other, rather than a result of fluctuations in composition of the secretion of the adrenal cortex.

The adrenal cortex responds remarkably promptly to the trophic action of ACTH. A few minutes after the administration of ACTH there occurs a measurable reduction in the concentration of ascorbic acid in the adrenal. Likewise, application of stress is followed within a few minutes by a depletion of adrenal ascorbic acid, a result of discharge of ACTH from the pituitary. Other indices of ACTH activity—depletion of sudanophilic substance, decrease in concentration of cholesterol and increase in glandular weight—also occur in response to stress. In man the sequence of metabolic events is such that the secretory activity of the adrenal cortex appears to reach a maximum by the third hour after intravenous administration of ACTH and returns to pretreatment activity by the sixth hour.⁶²

REGULATION OF PITUITARY ADRENOCORTICOTROPHIC ACTIVITY

Before we consider theories of pituitary regulation it must be emphasized that a most

* Attention is called to the fact that cortisone can induce sodium retention under certain conditions.

characteristic feature of the adrenal cortex is its responsiveness to a great variety of non-specific stresses. A relatively short period of apprenticeship in the field of adrenocortical physiology cools the ardor with which the novice greets the discovery that a drug, hormone or environmental change stimulates the pituitary-adrenocortical system. The demonstration that a substance induces an acceleration in the rate of discharge of ACTH from the adenohipophysis is of relatively little significance when considered alone. On the other hand, a finding of real significance is the demonstration that an agent, or the disruption of a neural or neurovascular path, or the destruction of a nucleus of nerve cells prevents or inhibits the accelerated rate of discharge of ACTH which normally accompanies the application of a stressful stimulus to the organism.

Evaluation of pituitary adrenocorticotrophic activity is no better than the index employed to assess such activity. The experimental studies on regulation which will be considered in the present review have with few exceptions been based on one or more of the following indices: adrenal weight, adrenal ascorbic acid, adrenal cholesterol, circulating lymphocytes, circulating eosinophils. The action of ACTH upon the adrenal cortex is manifested by an increase in weight of the gland and a decrease in its concentration of cholesterol and ascorbic acid. These three phenomena provide excellent indices of the rate of discharge of ACTH from the adenohipophysis in experimental animals. Adrenal weight is of particular value in experiments of relatively long duration. On the other hand, adrenal ascorbic acid and cholesterol are admirably suited to experiments of short duration.

Increased rate of discharge of ACTH stimulates the adrenal cortex to increased rate of secretion of cortical hormone, a substance which induces lymphocytopenia and eosinopenia. The determination of the number of circulating lymphocytes is particularly valuable for the assessment of ACTH discharge in rodents. The number of circulating eosinophils is the best index of adrenocortical activity in man. However, caution must be exercised in the interpretation of changes in the number of eosinophils, particularly when the organism is subjected to a severe degree of stress. It has been demonstrated that large doses of epinephrine induce an eosinopenia in patients with Addison's disease.⁵⁵

The measurement of 17-ketosteroids in the urine is of no value in assessing the rate of secretion of cortical hormone in man. Considerable confusion has arisen in the clinical literature due to misinterpretation of the significance of urinary 17-ketosteroids. There is a distinct difference between the pattern of urinary steroids in hypercorticism induced by ACTH administration and in adrenal hyperactivity induced by stress. In hypercorticism both corticoids and 17-ketosteroids are excreted at a rate greater than normal; in adrenal hyperactivity associated with stress the corticoids are increased but the 17-ketosteroids are usually decreased. (For a review of the literature see Sayers.⁶¹) The evidence indicates that the metabolic pathways concerned with the "utilization" and/or degradation of the cortical steroids undergo qualitative and possibly quantitative changes under the influence of stress.

After these preliminary remarks the subject of regulation of pituitary adrenocorticotrophic activity will now be discussed under the following headings: metabolites, cortical hormone, epinephrine and hypothalamus.

Metabolites. The adrenal cortex influences the concentration of a number of metabolites in the body fluids. The concentration of one or more of these metabolites may be a determining factor in the adenohipophyseal discharge of ACTH at a rate appropriate to the requirement of the organism for cortical hormone. Unfortunately, the pertinent studies are far too limited in scope to allow even tentative conclusions about this very important phase of the subject.

Ingle and Kendall³⁵ were unable, by altering the intake of sodium or potassium, to influence the changes in adrenal weight which accompany stress in rats. Administration of glucose prior to exposure to cold does not inhibit the increased rate of discharge of ACTH which normally follows such exposure.²¹ Glucose as well as adrenocortical extract will inhibit the adrenocortical stimulating effect of insulin.²¹ However, adrenocortical extract, in contrast to glucose, exerts a blocking action on insulin-induced pituitary activity without preventing the associated hypoglycemia.

Cortical Hormone. A considerable body of indirect evidence can be marshalled in support of the concept that the titer of cortical hormone in the body fluids regulates the rate of discharge of ACTH from the adenohipophysis. Adrenal

atrophy follows the chronic administration of adrenocortical extract (ACE)^{33,34} or DCA.^{16,59,70,80,81} DCA inhibits the hypertrophy of the adrenals which normally follows the application of a variety of non-specific damaging agents,⁶⁷ exercise,^{3,67} thyroxin,²⁹ estrogen² or electroshock-induced convulsions.⁸⁵ The adrenal hypertrophy which follows thyroxin administration⁸³ or exposure to low atmospheric pressure³⁸ is inhibited by treatment with ACE. In man withdrawal of DCA⁸⁶ or cortisone^{51,73} is followed by metabolic changes and symptoms characteristic of Addison's disease. These long-term experiments may be interpreted to mean that cortical steroid administration inhibits pituitary adrenocorticotrophic activity under both optimal and stressful conditions.

Ingle³² was able to show that the hypertrophy of the adrenal cortex of the rat, which normally occurs after twelve hours of forced exercise, does not occur when animals are treated with ACE throughout the period of exercise. Sayers and Sayers⁶³ have demonstrated that the decrease in concentration of adrenal ascorbic acid, which takes place one hour after the application of cold or heat, or after the injection of typhoid toxin, epinephrine or histamine, can be prevented by pretreatment of the animal with ACE or crystalline cortical steroids. ACE has been shown by Long and co-workers to inhibit the depletion of adrenal ascorbic acid which normally occurs after exposure to cold or after unilateral adrenalectomy⁴² or administration of epinephrine.⁴¹ ACE administered just prior to exposure to x-irradiation will prevent the early decrease in the concentration of adrenal cholesterol which otherwise follows such exposure.⁷⁵ The lymphocytopenic action of epinephrine can be inhibited by ACE.¹⁹ These numerous confirmatory observations, in which a number of different stresses and indices of adrenocortical activity are employed, strongly suggest that the great variety of non-specific stresses stimulate the adrenal cortex to activity by increasing the requirement of the organism for cortical hormone. Administration of cortical steroid obviates the necessity for the adrenal cortex to increase its secretory activity to meet the increased demands for hormone induced by stress.

Since the trophic action of ACTH on the adrenals of the hypophysectomized animal, as measured by increase in gland weight^{33,34} and ascorbic acid depletion,⁶³ is not influenced by administration of ACE, it is reasonable to

assume that cortical hormone acts to inhibit release of ACTH from the pituitary rather than to interfere with the action of the trophic on the adrenal cortex itself.

Discharge of ACTH in response to moderate stress may be completely or partially blocked depending upon the dose of cortical steroid administered. Furthermore, with increasing intensity of stress the amount of cortical steroid required to suppress pituitary adrenocorticotrophic activity becomes correspondingly greater.^{63,64} These quantitative relationships may be adequately explained if it is assumed that the rate of discharge of ACTH from the adenohypophysis fluctuates in accordance with the varying requirements of the organism for cortical hormone, i.e., the pituitary-adrenocortical system maintains the tissues in a state of well being in regard to adrenocortical hormone ("eucorticism") under either optimal or stressful conditions.

Pretreatment with cortical hormone fails to block accelerated discharge of ACTH when the animal is exposed to severe stress. Pretreatment with relatively large doses of cortical steroid partially but not completely blocks the reduction in adrenal ascorbic acid which normally occurs when rats are given large doses of histamine.⁶³ Administration of ACE prevents the decrease in concentration of adrenal cholesterol which occurs in the first few hours after x-irradiation but fails to prevent the late adrenal changes.⁷⁵ Depletion of cholesterol in the adrenals of rats infected with *Past. tularensis* is uninfluenced by large doses of ACE given at frequent intervals.⁶² DCA prevents adrenal hypertrophy which normally occurs in the fasted rat¹³ but neither DCA¹³ nor ACE^{11,12} prevents the hypertrophy caused by fasting in the guinea pig. Moya and Selye⁴⁸ and Gersberg et al.²¹ have failed to confirm the finding of Sayers and Sayers⁶³ that DCA prevents the depletion of adrenal ascorbic acid which normally follows the application of stressful stimuli. The following explanations of these divergent experimental results may be considered. First, it is entirely possible that in the experiments in which complete inhibition of pituitary adrenocorticotrophic activity is not obtained insufficient quantities of cortical steroids were employed; rate of "utilization" of cortical hormone appears to be exceedingly fast during severe stress. Second, it may well be that the "cortical hormone titer" mechanism is the only one at work in mild

to moderate degrees of stress whereas in more severe degrees of stress other mechanisms may play a complementary role to accelerate the rate of discharge of ACTH. Third, in severe stress with accompanying cardiovascular collapse, anoxia or accumulated toxins may act directly upon the cells of the adenohypophysis to increase their permeability to ACTH.

In conclusion the titer of cortical hormone in the body fluids appears to play a major role in the regulation of pituitary adrenocorticotrophic activity. The concept emphasizes the determining role which the peripheral tissues, by their rate of "utilization" of cortical hormone, exert in regulating pituitary adrenocorticotrophic activity. On the other hand, it minimizes the role of central mechanisms which induce ACTH discharge without regard to tissue needs for cortical hormone. The exact nature of the process by which the concentration of cortical hormone in the blood influences the rate of discharge of ACTH from the adenohypophysis is unknown; it is here that the "cortical hormone-titer" concept is particularly vague.

Epinephrine. The close anatomic approximation of the adrenal medulla and cortex as well as the fact that they both play important roles in homeostasis naturally leads to some speculation regarding a possible integrative functional relation between the sympatho-adrenal and the pituitary-adrenocortical systems.

Epinephrine may act to induce discharge of ACTH from the adenohypophysis by any one or a combination of the following mechanisms: (1) epinephrine may act directly on the adrenal cortex; (2) epinephrine may act directly on effector cells in the adenohypophysis or in the hypothalamus (hypothalamic stimulation could in turn activate the adenohypophysis); (3) epinephrine may act like other non-specific agents and stresses to increase tissue "utilization" of cortical hormone with a consequent lowering of venous blood titer of the hormone; (4) epinephrine may be the denominator common to all types of stress and the specific agent which promotes "utilization" of cortical hormone by the tissues.

Vogt,⁸² from studies on the biocorticoid (cold-protection test) content of adrenal vein blood, reached the conclusion that epinephrine has a direct stimulatory influence upon the adrenal cortex. However, her experiments do not rule out the possibility that epinephrine acts via the adenohypophysis to bring about a discharge of

ACTH. Necessary but not sufficient evidence for the direct action thesis is the observation that epinephrine induces a lymphocytopenia in the hypophysectomized rat⁸¹ and an eosinopenia in the hypophysectomized mouse.⁷² Long and Fry⁴³ have demonstrated that epinephrine does not induce depletion of adrenal ascorbic acid in the hypophysectomized rat. ACTH, but not epinephrine, stimulates the production of chemocorticoids by the isolated perfused adrenal gland.²⁷ On the basis of the more reliable studies it is concluded that epinephrine does not have a direct stimulatory action on the adrenal cortex.

Sayers and Sayers⁶⁴ have shown, and Long⁴¹ has confirmed, that the reduction in adrenal ascorbic acid produced by epinephrine can be prevented by administration of cortical steroid. The lymphocytopenic action of epinephrine is prevented by cortical steroid treatment.¹⁹ These observations strongly suggest that epinephrine, at least in small doses, acts like other non-specific stresses and does not have a direct action upon the pituitary.

Neither dibenamine, an agent which blocks the excitatory effects of both sympathin and epinephrine,⁴⁹ nor tetraethylammonium bromide, a substance which blocks autonomic ganglia,¹ influences the reduction in adrenal ascorbic acid which takes place in the rat in response to acute stress.⁷⁶ The lymphocytopenia of tourniquet shock is actually of greater magnitude in rats treated with dibenamine than in animals not so treated.⁸⁴ These observations do not lend support to a direct action of epinephrine on the adenohypophysis or associated structures; negative experiments of this nature are not conclusive since it is possible that the action of epinephrine on pituitary effector cells is not influenced by the autonomic blocking agents employed although Sawyer et al.⁶⁰ claim that dibenamine blocks the copulation-induced release of ovulating hormone from the adenohypophysis.

The completely sympathectomized animal is an important experimental tool which has not yet been fully exploited in the elucidation of the role of the sympatho-adrenal system in the regulation of pituitary-adrenocortical activity. It would be of great interest to know the comparative responses of the adrenal cortex of intact and sympathectomized animals to a variety of both acute and chronic types of stress. The completely sympathectomized dog shows a normal eosinopenic response to the injection of

formaldehyde.⁵⁶ Cannon⁶ has demonstrated that the sympathectomized cat is hypersensitive to various environmental exigencies. However, the degree of hypersensitivity does not approach that of the adrenalectomized animal. The completely sympathectomized dog is hypersensitive to insulin but resists heat, cold and anoxia almost as well as do intact control animals.⁴⁷ Furthermore, the sympathectomized dog is capable of maintaining normal blood sugar levels during exercise.⁴ Homeostasis is not significantly impaired by total sympathectomy in man.⁵⁴ These studies suggest that acceleration of adrenocortical activity in response to acute stress is not dependent upon the activity of the sympatho-adrenal system; neither does it appear that epinephrine is essential for the action of adrenocortical hormone on effector cells since the addition of epinephrine to an infusion of ACE does not improve the muscular work performance of adrenalectomized rats over that of similar animals given ACE alone.³⁶

McDermott et al.⁴⁶ have demonstrated that a transplant of the adenohipophysis will respond to the direct application of epinephrine with release of ACTH. They interpret their findings together with those of Ingle et al.,³³ Sayers and Sayers,⁶⁴ Cheng and Sayers⁷ and Recant et al.⁵⁶ to mean that there is "... a dual mechanism controlling the release of ACTH, one phase of which depends on the activation of the sympathetic nervous system, and the other on the utilization of adrenal cortical hormones (ACH) in the body." Long and associates^{41,42,46} have pointed out that both the sympatho-adrenal and pituitary-adrenocortical systems are stimulated to increased activity by a great variety of stressful conditions, and they are inclined to the view that epinephrine "... is not in the usual sense 'a non-specific agent.'" They state, "The stimulation of the elements of the autonomic nervous system with concomitant release of epinephrine that occurs under a variety of conditions appears to be a major factor in the activation of the adrenotrophic secretion from the anterior lobe." Also, "From the adrenal medullae the epinephrine appears to be carried to the anterior lobe where it acts directly upon secretory cells to stimulate the release of adrenocorticotrophic hormone." The release of ACTH from adenohipophyseal tissue by direct application of epinephrine is indeed an important contribution to the problem of pituitary regulation. However, it must be demonstrated that epinephrine has a

relatively specific action on pituitary transplants before it can be concluded that epinephrine plays a *special* role in the regulation of pituitary adrenocorticotrophic activity. For example, the experiment would have no special significance for epinephrine if the direct application of other vasoactive drugs induces release of ACTH from a transplant.

Certain experiments are difficult to reconcile with the "direct action of epinephrine" thesis. Adrenal denervation in the rabbit does not inhibit the lymphocytopenia which follows painful stimulation of the subcutaneous tissues¹⁵ and complete sympathectomy in the dog does not interfere with the eosinopenic response to formaldehyde injection.⁵⁶ The adrenal-demedullated rat responds promptly to stress with increased activity of the cortex.²⁴ Finally, Hume and Wittenstein³⁰ claim that certain discrete lesions in the hypothalamus block the normal eosinopenic response to epinephrine in animals with an intact adenohipophysis.

It is recognized that discharge of epinephrine contributes to the increase in the adrenocorticotrophic activity of the adenohipophysis in numerous acute stresses. However, the common association of discharge of epinephrine and increased secretory activity of the adrenal cortex does not help to answer the important question as to whether the action of epinephrine is a necessary and essential link in the series of events which lead to increased secretion of cortical hormone during stress or whether epinephrine acts like other non-specific stresses to increase the needs of the tissues for cortical hormone. Furthermore, it is recognized that large toxic doses of epinephrine may very well have a direct action on the adenohipophysis to release ACTH, an action which may be shared by other toxins.

Hypothalamus. Section of the infundibulum does not interfere with the response of the pituitary to acute stress in the rat^{8,18} or in the dog⁵⁶ or with the response to chronic exposure to cold in the rat.⁷⁸ These experiments, which demonstrate that the adenohipophysis is not dependent upon direct neural connections with the hypothalamus, are in keeping with the anatomic fact that few or no nerve fibers pass from the hypothalamus into the pars distalis. However, the experiments do not rule out the possibility that a vascular connection, the so-called "hypophyseal portal system," plays a role in the regulation of adrenocorticotrophic activity. Of interest in this regard is the demonstration^{25,26}

that the hypophyseal portal system regenerates after stalk section. Furthermore, de Groot and Harris¹⁵ and Hume and Wittenstein³⁰ have presented evidence which suggests that hypothalamic centers have a regulatory influence over pituitary adrenocorticotrophic activity. According to Hume and Wittenstein³⁰ lesions in the supraoptic nuclei of the dog did not alter the eosinopenic response to stress. On the other hand, paramedian lesions in the anterior hypothalamus and at the juncture of the middle and posterior hypothalamus abolished the usual eosinopenic response of the dog to epinephrine and insulin. The response to operative trauma was inhibited but not abolished. Despite the indication of inertia of the pituitary-adrenocortical system, on the basis of the eosinophil test, the dogs were not hypersensitive to insulin. Lateral or unilateral median hypothalamic lesions had no influence upon the eosinopenic response to stress in the dog.

According to de Groot and Harris¹⁵ stimulation of the posterior region of the tuber cinereum or the mamillary body but not of other regions of the hypothalamus or the hypophysis induced a lymphocytopenia in the rabbit. Lesions in the zona tuberalis and in the posterior region of the tuber cinereum or in the mammillary body abolished or diminished the lymphocytopenia of stress in the rabbit. Similar lesions in the posterior part of the pars distalis, pars intermedia or in the infundibulum did not influence the response to stress.

McDermott and associates⁴⁶ have demonstrated that diencephalic lesions (exact locus not given) in the rat interfere with the early (one hour after application of stress) eosinopenic response of the rat to a number of stressful stimuli. However, Long does not interpret these results to mean that the hypothalamus secretes a neurohumor which acts upon the hypothalamus, as do Hume and Wittenstein³⁰ and de Groot and Harris.¹⁵ Since section of the spinal cord below as well as above the site of a painful stimulus abolishes the eosinopenic response to stress, Long considers the hypothalamus to be the mediator of epinephrine release from the medulla. Stressful stimuli act through afferent nerves to stimulate the hypothalamus which in turn brings about the discharge of epinephrine via efferents to the adrenal medulla. Furthermore, McDermott et al.⁴⁶ have demonstrated that diencephalic lesions do not inhibit the second phase of the discharge of ACTH which

is considered by Long to be due to an increased rate of "utilization" of cortical hormone.

Transplants of the adenohypophysis in the anterior chamber of the eye will discharge ACTH in response to stress.^{9,18,46} It appears that neither direct neural nor neurovascular connections with the hypothalamus are essential for the discharge of ACTH from the adenohypophysis, although the possibility that the hypothalamus has a modifying influence upon pituitary adrenocorticotrophic activity has not been ruled out.

McDermott and associates⁴⁶ explain the results of Recant et al.⁵⁶ who found that sodium pentobarbital acts to stabilize the eosinophil count, and those of Sayers and Sayers,⁶⁴ who noted that barbiturate anesthesia prevents the adrenal cortical response to cold, as a selective action of barbiturates upon the hypothalamus. However, it has been demonstrated that barbiturate anesthesia will inhibit the response to cold^{58,64} but not to epinephrine,⁶⁴ histamine,⁶⁴ hemorrhage⁵⁸ or heat.⁵⁸ Laparotomy induces an eosinopenia in rats anesthetized with sodium pentobarbital⁴⁶ although Roche and associates⁵⁷ have found that spinal anesthesia in man inhibits the eosinopenia which follows operative trauma. According to Sayers and Sayers⁶⁴ barbiturate acts specifically in cold to prevent shivering, an activity of skeletal muscle which is associated with increased rate of "utilization" of cortical hormone. The results of additional experiments designed to evaluate the influence of barbiturate anesthesia upon the response of the pituitary-adrenocortical system to a variety of stresses are awaited with interest. The evidence at present available indicates that barbiturate inhibits the response of the pituitary to only one or at most a few specific types of stress; it does not support the thesis that the hypothalamus is an essential element in the regulation of pituitary ACTH activity.

COMMENTS

The secretory activity of the adrenal cortex is determined by the rate of discharge of ACTH from the adenohypophysis. In the absence of the pituitary the adrenal cortex secretes a small amount of cortical hormone at a steady rate. No incontrovertible evidence has been presented to support the thesis that the glomerulosa zone of the adrenal cortex secretes a "salt-active" hormone independent of pituitary control. Probably in man and in most experimental

animals only one trophin, ACTH, has a direct stimulatory action upon the adrenal cortex.

ACTH appears to be a polypeptide, the molecular weight and amino acid composition of which are still unknown.

The titer of cortical hormone in the body fluids influences the rate of discharge of ACTH from the adenohypophysis. The exact mechanism by which the cortical hormone inhibits the adenohypophysis is unknown. The action may be direct or it may be mediated by a metabolite whose concentration in the blood is determined by cortical hormone activity. In severe stress, anoxia or toxins may act directly on the adenohypophysis to induce discharge of ACTH.

The fact that adenohypophyseal transplants discharge ACTH in response to stress indicates that direct neural or neurovascular connections are not essential elements in the regulatory scheme. However, the experiments do not rule out the possibility that the hypothalamus has a modifying influence upon pituitary adrenocorticotrophic activity. Certain lesions in the hypothalamus appear to interfere with the normal response of the adrenal cortex to stress as measured by eosinopenia and lymphocytopenia.

The common association of sympatho-adrenal and pituitary-adrenocortical activity in response to stress is circumstantial evidence in favor of the view that epinephrine plays a special role in the discharge of ACTH. However, the results of studies from various laboratories, which involve completely sympathectomized, adrenal-demedullated and adrenal-denervated animals, appear to be incongruous. The direct action of epinephrine to induce discharge of ACTH from an adenohypophyseal transplant has important implications. However, it would be premature to conclude that epinephrine has a *special* regulatory role until it is demonstrated that the action of epinephrine on the transplant is not shared by other vasoactive agents.

A neurohumor of great practical importance would be one which acted directly on the adenohypophysis to accelerate the rate of discharge of ACTH independent of the concentration of cortical hormone in body fluids. Such a substance would produce clinical hypercorticism, a condition which induces remission in those diseases of connective tissues amenable to ACTH and cortisone therapy. Although the writer is skeptical that such a neurohumor will be found, he is convinced that the search for it is indeed a worthy endeavor.

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The General Adaptation Syndrome and the Diseases of Adaptation*

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IN the following pages we shall attempt to present a concise synopsis of the principal facts concerning the general adaptation syndrome and the diseases of adaptation. We shall make no effort to survey the entire rather voluminous pertinent literature which has accumulated during the past fifteen years. This would be far beyond the scope of this symposium; besides, an exhaustive treatise of this subject appeared a short time ago.⁸ On the other hand, we wish to analyze in some detail all the principal criticisms which have been or should be levelled against our theory in order to show that some of these can be definitely refuted, on the basis of available data, while others must stand and be clearly formulated to single out those fields in which additional investigation is most urgently needed.

We decided upon this manner of presentation because most of the established facts concerning the "stress problem" in general and the general adaptation syndrome in particular have come to light as a result of experiments based upon a rather novel and unorthodox concept of disease which in order to remain fruitful must constantly be checked against (and sometimes adjusted to) the new facts as they become known.

PRINCIPAL FACTS AND THEIR INTERPRETATION

Animal experiments performed in the course of 1936 showed us that the organism responds in a stereotyped manner to a variety of widely different agents such as infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue or x-irradiation. The specific actions of all these agents are quite different. Their only common feature is that they place the body in a state of stress. Hence we concluded that the stereotyped response, which is superimposed upon all specific effects, represents a reaction to stress as such.

The first manifestations of this stress response were: adrenocortical enlargement with histologic signs of hyperactivity, thymicolymphatic involution with certain concomitant changes in the blood count and gastrointestinal ulcers, often accompanied with other manifestations of damage or "shock." We were struck by the fact that, while during this reaction all the organs of the body showed involutional or degenerative changes, the adrenal cortex actually seemed to flourish on stress. We suspected this adrenal response to play a useful part in a non-specific adaptive reaction which we visualized as a "call to arms" of the body's defense forces and named the "alarm-reaction."¹ Later investigations revealed that the alarm reaction is merely the first stage of a much more prolonged *general adaptation syndrome*. The latter comprises three distinct stages, namely, the *alarm reaction* in which adaptation has not yet been acquired, the *stage of resistance* in which adaptation is optimal and, finally, the *stage of exhaustion* in which the acquired adaptation is lost again.

The experimental analysis of the mechanism of this syndrome was carried out as follows: Animals were adrenalectomized and then exposed to stressor agents. This showed us that in the absence of the adrenals stress can no longer cause thymicolymphatic involution or characteristic blood count changes. When adrenalectomized animals were treated with the impure cortical extracts available at that time, it became evident that thymicolymphatic involution and blood count changes could be produced by adrenal hormones even in the absence of the adrenals. The latter therefore were considered to be indirect results of stress mediated by corticoids. On the other hand, the gastrointestinal ulcers and other manifestations of damage were actually more severe in adrenalectomized than in intact animals and could be

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lessened by treatment with cortical extracts. It was concluded that these lesions are not mediated by the adrenal and are combatted by an adequate adrenocortical response to stress.²

In 1937 we found that hypophysectomy prevents the adrenal response during the alarm reaction and concluded that stress stimulates the cortex through the adrenocorticotrophic hormone ACTH.³

Later, when pure cortical steroids became available, we could show that administration of *mineralo-corticoids* (such as desoxycorticosterone) produce experimental replicas of the so-called hypertensive and rheumatic diseases, notably, nephrosclerosis, hypertension, vascular lesions (especially periarteritis nodosa and hyalin necrosis of arterioles)⁴ as well as arthritic changes resembling, in acute experiments, those of rheumatic fever and, after chronic treatment, those of rheumatoid arthritis.⁵ Yet even very high doses of mineralo-corticoids did not induce any noteworthy thymicolymphatic or blood count changes.

Significantly exposure of animals to non-specific stressor agents (e.g., cold) produced marked adrenocortical enlargement and organ changes very similar to those elicited by the administration of mineralo-corticoids.⁶

Glucocorticoids (such as cortisone), on the other hand, were highly effective in causing thymicolymphatic involution and in eliciting the characteristic blood count changes of the alarm reaction. Furthermore, they tended to inhibit the hypertensive and rheumatic changes which could be elicited in animals by mineralo-corticoids. Thus in many respects the two types of corticoid hormones antagonize each other.^{7,8}

Inflammatory granulomas, especially those produced in the vicinity of joints by the local application of irritants (e.g., formalin, mustard powder) as well as certain allergic reactions are also aggravated by mineralo-corticoids and prevented by glucocorticoids. Apparently the response of the adrenal cortex is most important not only in defense against systemic stress (affecting the whole organism) but also in the manifold topical defense reactions which occur upon exposure to local stress (e.g., bacterial or chemical irritants, responses of a "shock organ" to an allergen).^{8,9}

It was also observed that crude anterior pituitary extracts¹⁰ or lyophilized anterior pituitary tissue (LAP)⁷ duplicate the aforementioned actions of mineralo-corticoids upon the

cardiovascular system, blood pressure and kidneys. The hypophyseal preparations which we used were definitely corticotrophic in that they enlarged the adrenal cortex, but they were also rich in the so-called "growth hormone" or somatotrophic hormone (STH). As soon as we were able to obtain purified ACTH it became evident that the aforementioned pathogenic actions of the crude anterior pituitary preparations could not be due to their ACTH content since even the highest tolerable doses of the latter hormone failed to duplicate these effects. On the other hand, overdosage with pure STH caused cardiovascular and renal lesions identical with those previously observed in animals treated with mineralo-corticoids. It was concluded that the aforementioned actions of our crude anterior pituitary preparations were due to their STH content. It remains to be seen to what extent STH acts indirectly, by stimulating the mineralo-corticoid production of the adrenal cortex or directly by sensitizing the peripheral tissues to mineralo-corticoids. Preliminary observations suggest that both these mechanisms are implicated.¹¹

We conclude that the pathogenicity of many systemic and local irritants depends largely upon the function of the hypophysis-adrenocortical system. The latter may either enhance or inhibit the body's defense reactions against stressor agents and we think that derangements of this adaptive mechanism are the principal factor in the production of certain maladies which we therefore consider to be essentially diseases of adaptation.

Among the derangements of the general adaptation syndrome which may cause disease the following are particularly important: (1) an absolute excess or deficiency in the amount of corticoids and STH produced during stress; (2) a disproportion in the relative secretion, during stress, of ACTH and glucocorticoids on the one hand and of STH and of mineralo-corticoids on the other; (3) production by stress of metabolic derangements which abnormally alter the target organ response to STH, ACTH or corticoids (through the phenomenon of "conditioning"), (4) finally, we must not forget that although the hypophysis-adrenal mechanism plays a prominent role in the general adaptation syndrome, other organs which participate in the latter (e.g., nervous system, liver, kidney) may also respond abnormally and become the cause of disease during adaptation to stress. (Fig. 1.)

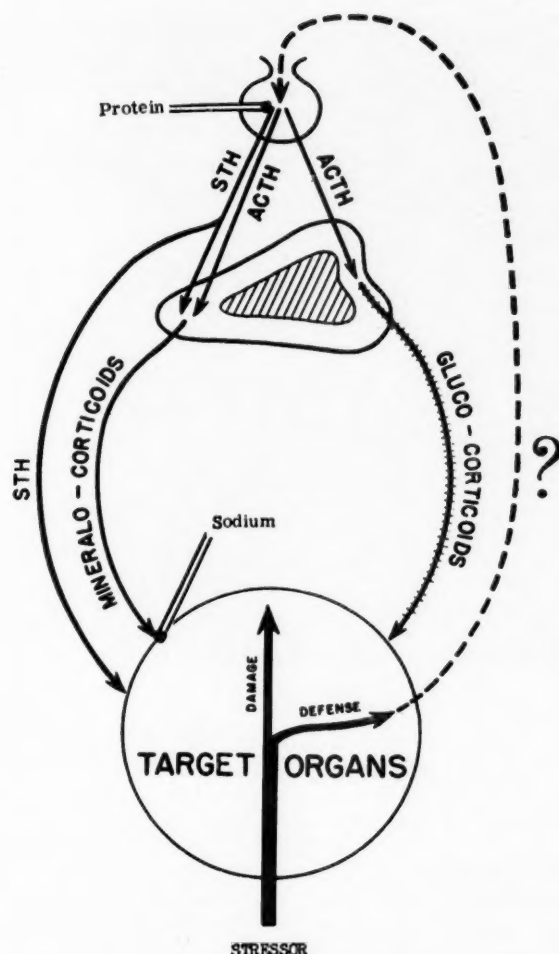


FIG. 1. Schematic diagram illustrating the principal interrelations between the hypophysis, the adrenal cortex and the peripheral target organs during the general adaptation syndrome. (Slightly modified after Selye.¹²) The stressor (trauma, infection, burns, etc.) acting upon the cells evokes a stimulus which induces the anterior pituitary to produce ACTH; under certain circumstances it may also cause a discharge of STH. The nature of this first mediator between the directly injured organ and the anterior pituitary is not yet known (humoral, nervous?); hence, it is indicated merely by an interrupted line, labelled with a question mark. ACTH induces the adrenal cortex to produce predominantly *gluco-corticoid* compounds the effect of which upon the response of the various target organs is generally inhibitory (e.g., catabolism, diminution of granuloma formation and of allergic responses). Conversely, STH enhances a variety of defensive reactions in the target organs (e.g., anabolism, augmentation of granuloma formation and of allergic responses), primarily by stimulating the connective tissue. Part of this action is undoubtedly not mediated through the adrenal cortex but this direct effect sensitizes the connective tissue elements to the essentially similar actions of the *mineralo-corticoids*. It is probably that STH also acts by increasing the production of mineralo-corticoids. However, in itself it cannot maintain the cortical cells in a responsive condition, hence its

PRINCIPAL CRITICISMS OF THE GENERAL-ADAPTATION-SYNDROME CONCEPT

Desoxycorticosterone (DCA) may not occur in the adrenals. The fundamental work concerning the diseases of adaptation has been performed in animals treated with excesses of DCA. It is this work which led to the concept that diseases could be due to an excessive mineralo-corticoid production. Evidence now at hand is insufficient to prove with certainty that desoxycorticosterone is produced as such by the adrenal cortex. On the other hand, observations on adrenals perfused *in vitro* strongly suggest that desoxycorticosterone is discharged into the venous effluent.¹³

It will be recalled that LAP (a mineralo-corticotrophic extract) also causes similar lesions in intact although not in adrenalectomized animals. (Figs. 2 to 4.) Even if desoxycorticosterone itself were not secreted by the adrenal cortex, the aforementioned observations would still strongly suggest that some similarly acting principle is produced as a result of hypophyseal stimulation. Furthermore the "amorphous fraction" of Kendall, the "sodium factor" of Hartman and desoxocortisone have all been shown to possess typical mineralo-corticoid actions. All these substances have been prepared from the adrenals by several investigators and in good yields so that there can be no question about their being natural products of adrenal activity.

The doses of DCA used in the fundamental experiments on the "diseases of adaptation" may exceed the amounts produced endogenously by the adrenal itself. This criticism has been voiced particularly with regard to the earliest experiments, in which DCA was given in the form of injections to non-sensitized animals. Subsequently, with the introduction of the pellet implantation technic, especially in animals sensitized by unilateral nephrectomy and/or high sodium diets, much

"corticotrophic" effect is dependent upon the simultaneous availability of ACTH. In the final analysis the physiologic and pathologic responses of the target organs to stressor agents largely depend upon the balance between the mineralo-corticoids and STH on the one hand and ACTH and the *gluco-corticoids* on the other. The entire reaction is highly subject to what we called "extraneous conditioning factors" (individual variations of organ susceptibility, heredity, diet, previous exposure to stress). Among these particular attention has been given to *dietary protein* which appears to increase the production and/or activity of STH and to *sodium* which augments the effects of mineralo-corticoids upon certain target organs, especially the kidney.

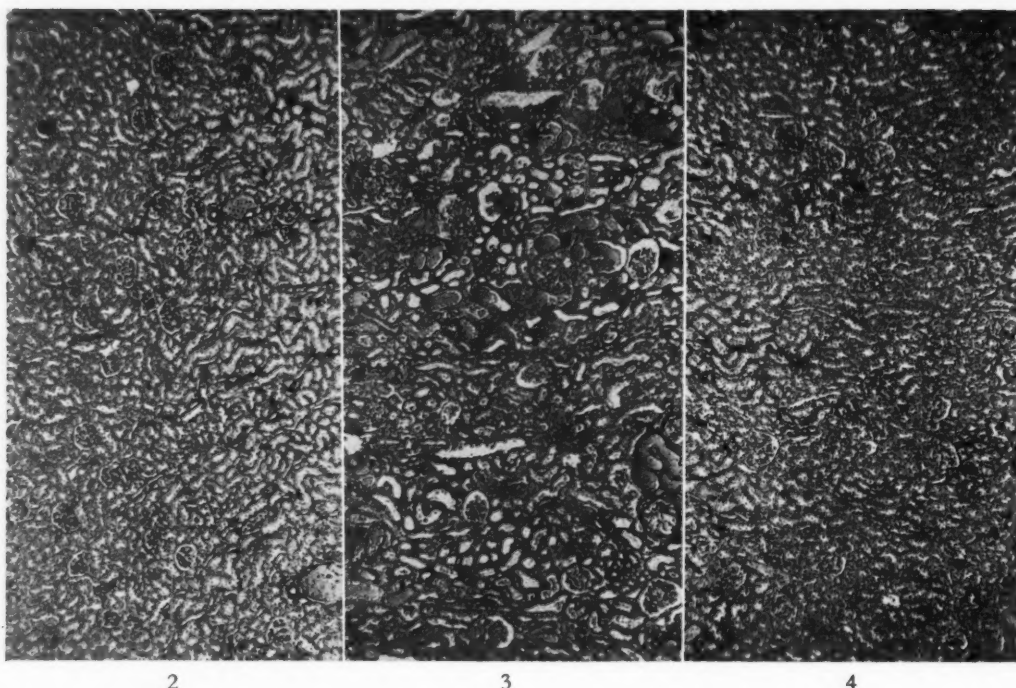


FIG. 2. Kidney of a normal control rat.

FIG. 3. Kidney of a rat simultaneously overdosed with LAP and cortisone. Note that the intense proteinuria led to diffuse hyalin cast formation and dilatation of the tubules. The glomeruli are greatly enlarged and hemorrhages are seen in the spaces of Bowman's capsules. Many of the glomerular loops are hyalinized. All of the animals in this group had died or were killed in a moribund condition within twenty-four days of treatment.

FIG. 4. Kidney of an adrenalectomized rat treated with LAP and cortisone (in the same manner as that whose kidney is shown in Figure 3). Note that the renal hypertrophy (due to a direct action of the STH in our pituitary extract) is quite pronounced but there is no sign of actual renal damage. The glomeruli are not hyalinized, Bowman's capsules contain no hemorrhages and there is no hyalin cast formation.

smaller amounts of the hormone proved to be disease producing.

Recent experiments in which threshold doses of DCA and STH were given alone or in combination are particularly illuminating in this respect. They showed that even comparatively small doses of STH are effective in sensitizing the rat to the cardiovascular and renal damage-producing action of DCA.¹⁴ Since, on the other hand, these same actions of STH are completely inhibited by large doses of cortisone,¹¹ it is obvious that the mutually antagonistic actions of gluco-corticoids (such as cortisone) and mineralo-corticoids (such as DCA) are largely dependent upon the amount of STH in the circulation. It is quite conceivable therefore that in individuals sensitized to the toxic actions of mineralo-corticoids by one or more of the aforementioned "conditioning factors" the syndrome of DCA overdosage may be elicited without any appreciable increase in the total urinary corticoid elimination.

It must be remembered furthermore that there is no objective reason to consider the pathogenic amounts of mineralo-corticoids as being beyond the limits of what could be produced in the body during stress. The quantities excreted in the urine of men who had received DCA in doses conducive to hypertension, increased blood volume, edema and renal damage do not exceed those eliminated by patients after burns, traumatic injuries or acute infections. If we can judge by the amounts of gluco-corticoids required to produce remissions in those spontaneous diseases which have been simulated in the animal by DCA overdosage, this criticism appears to be even more unjustified. About 10 mg. of DCA a day given over a period of weeks would certainly be pathogenic in man, while 80 to 100 mg. of cortisone is usually required to produce a pronounced remission, for instance, in rheumatoid arthritis or lupus erythematosus.

The urinary elimination of corticoids is not always

demonstrably abnormal in the diseases of adaptation. This objection has already been partly answered in the preceding passages. Furthermore, as we have repeatedly emphasized in this paper, diseases of adaptation do not necessarily result from an absolute deficiency or excess of corticoids; they can also ensue as a consequence of an improper balance between gluco- and mineralo-corticoid secretion or by a state of "relative hypocorticism." Thus in our "topical irritation arthritis" the introduction of an irritant into the joint region produced a violent arthritis in perfectly normal animals, yet it failed to do so after pretreatment with an excess of ACTH or cortisone. This clearly shows that the adequacy of corticoid production can be assessed only in proportion to the pathogen which creates a need for such hormones. It is highly probable that pathogenic factors which cause disease in individuals whose corticoid production remains "normal" would fail to do so if the adrenals responded with an increase in hormone discharge commensurate with the increased requirements occasioned by an abnormal situation. Indeed it is quite possible that many individuals who carry the pathogens (whatever these may be) of rheumatoid arthritis, allergies, lupus erythematosus and so forth can remain in perfect health throughout life because through the general adaptation syndrome mechanism they have rendered these potential pathogens quite innocuous. To use an analogy from an entirely different field, one might compare them with the typhoid or meningococcus carrier who lives in perfect harmony with the deadly germs present in his body.

Quite recently we observed (Selye, unpublished) that transitory overdosage with LAP and DCA during a period of two weeks elicits a progressive and eventually fatal nephrosclerosis and hypertension in the rat. Many of the animals so treated appeared to be in excellent health and continued to gain weight at a normal rate after discontinuance of the hormone administration; yet eventually they died with the typical lesions characteristic of our "diseases of adaptation." Such observations suggest that a transitory episode of excessive STH and/or mineralo-corticoid production may cause the appearance of disease manifestations at a time when the increase in the production (and hence excretion) of the causative hormones no longer exists. This finding is somewhat reminiscent of the well known fact that partial constriction of one renal artery may

cause a persistent hypertension which progresses even after the clamped kidney is removed.

It should be mentioned furthermore that some evidence of an anomaly in steroid metabolism has been noted in patients suffering from the rheumatic-allergic diseases (e.g., increased pregnandiol excretion after the administration of progesterone, anomalies in 17-ketosteroid elimination).

Research along these lines has been handicapped, principally because of the difficulty of assaying blood or urine specifically for mineralo-corticoid activity. However, several recently published improvements in technic hold great promise for elucidation of this important problem.

Why are the "diseases of adaptation" so polymorphic in their manifestations if they are all due to stress? We believe that the principal reasons for this polymorphism are the so-called "conditioning factors" (Fig. 1), namely, the specific effects of the evocative stressors and other exogenous or endogenous factors (heredity, pre-existent disease of certain organs, diet, previous exposure to stress, etc.) which can affect, selectively, certain pathways or target organs of the general adaptation syndrome response.

Why does exposure to the same stressor produce disease only in certain individuals? It is undoubtedly true that the same drug, microbe, emotional irritant or physical injury may produce a disease of adaptation in one person and be tolerated with impunity by another. It should be recalled, however, that the general adaptation syndrome is a useful and normal physiologic reaction to stress; only its derangements have been interpreted as diseases of adaptation. Hence exposure to a stressor can be expected to produce such diseases only if the defense reaction is inadequate. Thus, for instance, in our experimental efforts to produce the hyalinosis-hypertension syndrome in rats by exposure to cold we found it necessary to perform unilateral nephrectomies and to keep the animals on high sodium, high protein diets. All these conditioning circumstances failed to produce disease in the absence of stress but upon exposure to cold they caused a derangement of the general adaptation syndrome, with consequent cardiovascular lesions, nephrosclerosis and a rise in blood pressure. It is very probable that in man, too, under the influence of stress, similar diseases would develop only when the general adaptation syndrome is prevented from evolving in a

normal manner, as a result of adverse conditioning factors.

The problem of the "first mediator." There is a striking paucity of information concerning stimuli which during stress induce the pituitary to discharge ACTH. Transection of the stalk (with all its nervous and blood vessel connections between hypophysis and hypothalamus) does not necessarily impede this response. The nervous pathways between the hypothalamus and the pituitary may be of importance in the event of exposure to purely neurogenic stressors; it remains to be seen, however, how the "stress message" is carried to the anterior lobe from a burned skin, a traumatized limb or tissues damaged by systemic infections and intoxications. We expressed the opinion that perhaps an ACTH discharge could be caused by any derangement in the chemical or physical characteristics of the blood but this is merely a hypothesis.¹⁵ Further work along this line is badly needed.

There is no objective evidence of an STH discharge during stress. This objection has not yet been raised because our work on STH has only recently been published. Nevertheless we believed that this question should be clearly formulated. Up to now there was, of course, no inducement to attempt the demonstration of STH in the blood of patients suffering from what we call the diseases of adaptation; hence the lack of pertinent data is not surprising. It may take some time before we will have relevant data because the bioassay methods for STH in biologic fluids are cumbersome and inaccurate. It is definitely known, however, that the pituitaries of animals and man contain large amounts of STH, far beyond the period of growth, throughout adult life. It is tempting to assume that the elaboration of STH is useful not only for the promotion of somatic growth but also for the stimulation of the connective tissues in a sense directly opposite to the inhibitory effect of ACTH and glucocorticoids. STH might be especially useful in various types of infections in which defensive encapsulation and granuloma formation around the foci of pathogenic organisms may help to prevent a spread. Significantly in animals acute intoxication with large doses of STH reproduces a syndrome of splenic, hepatic and renal enlargement with proteinuria rather reminiscent of that seen in many systemic infections of man.¹¹ Yet at present there is no objective proof of any

increase in STH production during any kind of systemic stress.

SUMMARY AND CONCLUSIONS

Following a brief survey of the principal data relating to the general adaptation syndrome and the diseases of adaptation we attempted to evaluate critically the chief objections which have been or should be raised in connection with this concept.

In our opinion there is no reason to doubt that the organism responds with a stereotyped reaction pattern during stress situations elicited by a large variety of agents. This reaction, which we called the general adaptation syndrome, is principally concerned with adaptive adjustments to the stressor (or stress producing); it is therefore essentially a physiologically useful phenomenon.

We also conclude that derangements of this reaction pattern may result in diseases in which maladaptation (and particularly inadequate pituitary and/or corticoid hormone production) represents the major pathogenic factor.

We believe that it is of heuristic value to classify the ensuing maladies as "diseases of adaptation." It must be kept in mind, however, that all classifications of disease overlap. Rheumatic fever may be listed with equal justification among the infectious, cardiovascular or joint diseases; similarly an adrenogenital syndrome due to suprarenal carcinoma may be discussed under the headings of tumors, intersexuality, precocious puberty or hypercorticism.

It would undoubtedly be more precise, but also much more cumbersome, to refer to the so-called "diseases of adaptation" as "diseases in which a derangement of the general adaptation mechanism is the principal pathogenic factor." Be this as it may, problems of terminology are comparatively unimportant if the concept itself will continue to be useful in bringing to light new facts pertaining to the pathogenesis and therapy of disease.

In order to accomplish this aim further work appears to be most urgently needed in regard to (1) the identity of the "first mediator" which initiates the pituitary hormone discharge during stress; (2) hormone (especially ACTH, STH, corticoids) metabolism during the general adaptation syndrome; (3) actions between the hormones secreted during stress and the factors which affect the body's response to them ("conditioning factors").

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Role of the Adrenal Cortex in Intermediary Metabolism*

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WITH the rapid growth of knowledge resulting from the dramatic discovery of the ability of large amounts of adrenal hormone to modify certain disease processes, concepts concerning the physiologic role of the adrenal cortex in health and disease are in a state of flux. The apparent dichotomy between the therapeutic effectiveness and the metabolic actions of ACTH and cortisone in disease makes it abundantly clear that any attempt to interpret adrenal cortex action solely in terms of its role in intermediary metabolism will limit rather than extend our knowledge. To this writer the most useful working concept at present is that the adrenal cortex is concerned in some very fundamental way with the maintenance of homeostasis in the broadest sense, and that in so doing, the organism is being protected against stressful situations.¹⁻³ At the same time one must not lose sight of the fact that the adrenal cortex represents only one star in the constellation of endocrine factors concerned with the maintenance of homeostasis.⁴

The concept that the adrenal cortex operates to preserve homeostasis is based on two very general observations. The first relates to the unequivocal evidences of an increase in the level of secretion of the adrenal cortex demonstrable after almost any stimulus, regardless of its nature.⁵ The second concerns the fixed limits within which various metabolic and physiologic processes take place in the adrenalectomized animal. It is this fixation which is largely responsible for the high sensitivity of the adrenalectomized animal to every kind of stress. Well documented examples of this limitation are found in the disturbances of renal function of adrenalectomized animals or patients with Addison's disease. During adrenal insufficiency sodium and chloride are excreted at relatively constant high levels so that at low or normal

intakes salt loss and dehydration occur whereas high salt loads, which would be well tolerated by the normal organism, lead to salt retention and edema. Similarly, in the absence of the adrenal cortex water is excreted at a relatively constant low level and hence water loads which are adequately handled by normal subjects readily lead to water retention and intoxication. The appreciation of this role of the adrenal cortex in facilitating in some way the ability of the organism to respond to wide shifts in the internal and external environment should do much to simplify the interpretation of existing metabolic data.

In interpreting experimental studies on the role of the adrenal cortex or of any endocrine gland in metabolism there are certain fundamental considerations which must be kept in mind. Failure to do so is largely responsible for much of the contradictory data and interpretations present in the literature.

Of first importance is some concept of the position of the hormones in the hierarchy of factors controlling metabolism. Although there is no clear understanding yet as to precisely how hormones act, it is safe to say that their action is not basic to the metabolic reactions that they influence, i.e., no reaction is initiated or stopped by hormone presence or absence, only rates of existing reactions are modified. Whether this is done by influencing enzyme activity or by effecting cell permeability (and hence availability of specific substrates) or by some other mechanism remains to be answered. To maintain certain reaction rates hormones must be continually present. It is not known whether hormones are used up at the site of their action or elsewhere.

Experimental studies designed to elucidate hormone action usually involve either ablation of the gland in question or injection of large

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amounts of the hormone into intact or deficient animals. Since intermediary metabolism is controlled by a galaxy of hormones working in unison, phenomena resulting from ablation of one gland may be due as much to the unopposed action of other glands as to the specific deficiency induced. The relative significance of each of these sometimes can be determined only by further experiments involving double ablations. An example is provided by the tendency to hypoglycemia in the adrenalectomized animal which is due in part to the unopposed action of endogenous insulin and in part to the specific metabolic effects of adrenal insufficiency. Similarly, injection of large amounts of one hormone may stimulate the secretion of other hormones, some with antagonistic actions. One must distinguish between the effects of the injected hormone and those of the antagonist. Thus insulin in small doses or in the presence of adequate carbohydrate will stimulate protein anabolism. When marked or prolonged hypoglycemia follows insulin injection, evidences of increased protein catabolism occur, stimulation of the adrenal cortex apparently being partially responsible for the occurrence of the latter reaction.⁶

Furthermore, certain of the metabolic alterations which follow removal of a gland or administration of a hormone may be secondary to non-hormonal phenomena and not specific hormone effects. Thus some of the abnormalities in the metabolism of adrenalectomized or hypophysectomized animals allowed to eat *ad libitum* are due to the anorexia characteristic of these states. Conversely, the obesity sometimes seen in Cushing's syndrome or in patients receiving large amounts of ACTH or cortisone may be as much a reflection of an increased appetite and food intake as a specific effect on fat metabolism. Information must be derived both from experiments in which the food intake is controlled as well as those in which the subject is allowed to eat *ad libitum* in order to establish the precise roles of hormones and other factors in the observed responses. Another important and frequently ignored example of a non-specific effect relates to the metabolic consequences of the circulatory insufficiency often encountered in untreated adrenal insufficiency. Peripheral circulatory failure is characteristically associated with an accelerated rate of carbohydrate utilization with resultant depletion of carbohydrate stores due to the relative inefficiency of glycol-

ysis compared to oxidation of carbohydrate.⁷ Depletion of carbohydrate stores and the development of hypoglycemia during adrenal insufficiency may thus be due in part to the failing circulation so common in this preparation. The apparent improvement in carbohydrate tolerance of the adrenalectomized animal following treatment with desoxycorticosterone is undoubtedly more related to the circulatory effects of this steroid than to its metabolic effects.¹⁹ Peripheral circulatory failure is also associated with an increased rate of protein breakdown in the peripheral tissues and a decreased rate of deamination of amino acids in the liver.⁷ The former does not occur as readily in the adrenalectomized animal while the latter does and has been considered a specific defect in this preparation.

The dosage of hormone used in experimental work must always be considered when interpreting results in physiologic terms. It is well established now that directly or indirectly the metabolic effects of hormones at high dosage may be different from those following low dosage. Thus thyroxine when given to hypothyroid animals in small doses promotes growth (protein anabolism) while in large doses it inhibits the growth of normal or hypothyroid animals.⁸ Small doses of adrenal extract administered to force-fed adrenalectomized rats may induce a positive nitrogen balance, larger doses a negative nitrogen balance and inhibition of growth.⁹

Since it is a general rule in endocrinology that the administration of a hormone suppresses the endogenous secretion of that same hormone, it may be accepted that any metabolic effect of a hormone achieved in an intact animal is quantitatively or qualitatively an overdosage effect. In the strictest sense of the word only those doses of hormone that restore normalcy to the animal with an ablated gland may be considered as physiologic. Furthermore, it must be realized that the physiologic dose of a hormone cannot always be expressed in fixed quantitative units. Nowhere is this more true than in the case of the adrenal cortex in which the dose of hormone to maintain life, as the minimum requirement, varies greatly with circumstances. Under conditions of stress a dose of hormone may be required which under basal conditions would induce evidences of overdosage.¹

It follows as a corollary that not only may the measurable effects of a hormone under given

conditions be greatly influenced by the dosage used but also with the same dose of hormone the effects may be modified by changing the internal or external environment. Thus the same dose of adrenal extract may have a protein anabolic effect in adrenalectomized rats,⁹ may induce no measurable change in nitrogen metabolism in rats given ample carbohydrate, may have a small but significant catabolic effect in fasting rats or may induce a very striking increase in nitrogen metabolism in animals subjected to insulin hypoglycemia or other types of stress.^{3,6} These seemingly contradictory effects of adrenal hormone on metabolism focus attention on another concept of hormone action which is now receiving increasing attention. This is that the adrenal hormone is necessary but not responsible for a great variety of metabolic reactions some of which are specific or non-specific features of the response to stress in general. Thus Ingle, who has emphasized this point of view, has shown that the characteristic negative nitrogen balance which results from injury in intact but not in adrenalectomized animals also occurs in the latter when they are receiving a constant maintenance dose of adrenal hormone which itself does not alter nitrogen metabolism in the unstressed animal.¹⁰ Many other examples of this same type of phenomenon may be found in both the old and recent literature.^{3,11-18,30} Thus in contrast to adrenalectomized animals who do not respond normally adrenal extract-maintained adrenalectomized animals may react to various stimuli precisely as do animals with intact adrenal glands. The magnitude of endogenous secretion of adrenal hormone in the latter animals in response to these stimuli is, therefore, not responsible for the effects observed but the presence of adrenal hormone is necessary for the response to occur.

From such studies one may seriously raise the question whether the adrenal cortex itself has any direct effect on metabolism or whether it simply facilitates reactions which are determined by other hormones or stimuli, generally stressful. Since large doses of adrenal hormone induce definite metabolic responses even in the absence of obviously stressful stimuli, the possibility has been considered that the so-called overdosage effects of adrenal hormone may in fact represent the effects of an oversensitive response to minor stresses which would have no metabolic impact in the presence of smaller amounts of hormone.³ The animal receiving

excess adrenal hormone or the patient with Cushing's syndrome might thus be considered to be organisms mobilized to respond to even the slightest change in external or internal environment.

With these considerations in mind we may now go on to an interpretation of the roles of the adrenal cortex in carbohydrate, protein and fat metabolism. It is apparent from the former discussion that the most logical approach will be to consider separately the metabolism of the adrenal insufficient organism with and without hormone maintenance and the metabolic effects of adrenal hormone overdosage. An interpretation of what are the physiologic effects of the adrenal cortex can be derived only by inference from these data since the metabolism of the intact organism, at rest and under stress, is what it is by virtue of the interplay of the secretions of the endocrine glands in physiologic amounts and proportions.

INTERMEDIARY METABOLISM DURING ADRENAL INSUFFICIENCY

The metabolism of the adrenal-insufficient organism is characterized by its inflexibility. This is most apparent in the control of the blood sugar. In the fasting state and particularly under conditions of stress, even when carbohydrate is available, the adrenalectomized animal's blood sugar falls progressively. The organism shows a highly inadequate ability to call into play those mechanisms by which the normal animal protects itself against carbohydrate deprivation. Carbohydrate utilization thus appears to be proceeding at a rate which is excessive in terms of the availability of carbohydrate from pre-formed stores and by gluconeogenesis. With an adequate diet, however, and in the absence of stress, which presumably increases carbohydrate needs, the rate of carbohydrate utilization falls in the same range as normal. Thus Russell showed that normal and adrenalectomized rats required the same rate of glucose infusion to maintain their blood sugar levels after functional hepatectomy (evisceration), provided the circulation of the latter was maintained with desoxycorticosterone.¹⁹ In the fasting eviscerated animal not maintained with glucose the rate of fall of blood sugar is more rapid in the absence of the adrenal cortex. Ingle and Nezamis²⁰ have demonstrated that the alteration in carbohydrate utilization by the adrenalectomized eviscerated rat includes an inability to tolerate large as well

as small loads of glucose compared to animals with intact adrenals. This then is another example of the fixation of physiologic processes between restricted limits in the absence of the adrenal cortex.

The precise nature of the disturbance in carbohydrate production and utilization in the adrenalectomized animal has not yet been elucidated although a good deal of information is available about certain aspects of the problem, notably the relation of the adrenal cortex to gluconeogenesis from protein. The liver glycogen levels of adrenalectomized animals decline rapidly on fasting in contrast to those of normal animals which fall more slowly under the same circumstances. Urinary nitrogen excretion remains low and there is evidence that endogenous protein is not readily available as a source for new carbohydrate.¹³ The fasted phlorhizinized adrenalectomized rat exhibits a lower than normal glucose and nitrogen excretion.²¹ Although some evidence has been presented to indicate that the adrenalectomized animal may have some difficulty in deaminating amino acids and converting 3-carbon precursors to liver glycogen,^{22,22a} the major defect in gluconeogenesis appears to be related to the difficulty in mobilizing endogenous protein for catabolism. Adrenalectomized animals can be maintained in good condition without hypoglycemia on high protein carbohydrate-free diets²³ and the glucose and nitrogen excretion of adrenalectomized phloridzinized rats on similar diets is not grossly abnormal. Under these circumstances carbohydrate must be derived from dietary amino acids. Injected amino acids appear to be converted to urea in the nephrectomized adrenalectomized rat as efficiently as in the normal.²⁴ Using N^{15} glycine as a tracer Hoberman was unable to detect any abnormality in amino acid catabolism in adrenalectomized rats.²⁵ Despite these evidences of a defect in carbohydrate production from endogenous protein it is apparent that this alone is insufficient to account for all the difficulty in maintaining the blood sugar. The suggestion has already been made that, under certain circumstances at least, there may also be a disproportionately high use of carbohydrate by the adrenalectomized animal. One of the more convincing evidences for this is found in the study of Ingle and Prestrud²⁶ on the alleviation of pancreatic diabetes by adrenalectomy, a phenomenon first reported by Long and Lukens in 1936.²⁷ The

former investigators showed that if the problem of the decreased food intake which generally follows adrenalectomy were avoided by the use of tube feeding, the diminished glycosuria could not be accounted for by the decline in nitrogen excretion that results from adrenalectomy. One must assume that either an increase in carbohydrate utilization or a decrease in carbohydrate production from non-protein sources must have occurred after adrenalectomy in the diabetic animal.

Carbohydrate utilization includes storage as glycogen, oxidation to carbon dioxide and water and conversion to fat and protein. Little definitive information is available at present concerning how each of these processes is influenced by adrenalectomy. Liver glycogen concentrations are generally very low while muscle glycogen levels fall moderately in adrenalectomized animals during fasting. Low liver glycogen levels, however, need not necessarily be interpreted as indicating impaired synthesis of glycogen. A relatively more rapid turnover of glycogen in the liver could equally well result in low concentrations. This remains to be demonstrated. Glycogen deposition measured *in vitro* with the aid of C^{14} labeled glucose has been reported low in diaphragms from adrenalectomized rats.²⁸

As already indicated, carbohydrate utilization other than storage as glycogen appears to be increased in the adrenal-insufficient organism. Measurements of the respiratory quotient in adrenalectomized animals have yielded no clues as to the composition of the increase in carbohydrate metabolism.¹⁹ In patients with Addison's disease, however, the fasting respiratory quotient has been reported to be higher than normal and after intravenous glucose to be over 0.90.²⁹ This suggests an increased utilization of carbohydrate either by oxidation or conversion to fat. Villee and Hastings²⁸ found an increased utilization of C^{14} labeled glucose by adrenalectomized rat diaphragm muscle. The amount of glucose converted to CO_2 was greater than normal but represented only a small proportion of the total glucose utilized but not stored as glycogen. The greatest part of the glucose utilized was unaccounted for but could conceivably be represented by conversion to fat, protein, lactate or other carbohydrate intermediaries. The only evidence for accelerated conversion of carbohydrate to fat in the adrenalectomized animal is found in the recent

report of Welt and Wilhelmi.³⁰ These investigators found that following adrenalectomy the female rat, eating a high carbohydrate, fat-free diet, showed a greater uptake of deuterium from deuterium oxide into the liver and carcass fatty acids than did intact controls. These results may be interpreted as indicating a more rapid conversion of carbohydrate to fat in this preparation.

Since the adrenalectomized animal is extraordinarily sensitive to insulin and this hormone has certain metabolic actions opposed to those of the adrenal cortex, it may be asked justifiably how much of the disturbance in carbohydrate metabolism is due to the unopposed action of insulin. While undoubtedly some of the observed phenomena in the adrenalectomized animal are due to relative hyperinsulinism, it is safe to say that the major part is due to insufficiency of adrenal hormone *per se*. This is attested to best by the fact that most of the characteristic features of the carbohydrate metabolism of adrenal insufficiency persist in the adrenalectomized pancreatectomized animal.

The alterations in protein metabolism in adrenalectomized animals have implications beyond those related to gluconeogenesis. The defect in protein metabolism in the adrenalectomized animal appears to be primarily at the level of whole protein, to be largely extrahepatic and to involve both an increased rate of protein synthesis and a decreased rate of protein breakdown. Protein anabolism has been demonstrated only with the aid of isotopic nitrogen.²⁵ The net effect on nitrogen metabolism is demonstrable in the lowered nitrogen excretion of the fasted adrenalectomized animal,¹³ the decreased rate of urea formation in the adrenalectomized-nephrectomized rat²⁴ and the lessened accumulation of amino acids in the plasma of hepatectomized-adrenalectomized rats.³¹ The implication of these findings is that the adrenalectomized animal should show a greater growth rate than normal. In practice this is not so as regards somatic growth, largely because the organism reacts to adrenalectomy by a decrease in appetite. Nevertheless, it has been found that the carcasses of normal rats restricted to the same food intake as adrenalectomized animals have a greater proportion of fat and a lesser proportion of water and protein than do the adrenalectomized animals, suggesting chemical growth in the latter.³² With adequate food intake, however, it would appear

that a small amount of adrenal hormone is necessary for optimal growth.⁹ On the other hand, there are evidences that specific tissues may show enhanced growth rates in adrenalectomized animals, notably lymphoid tissue and spleen,³³ hair³⁴ and epiphyseal cartilage.³⁵ In animals on a high protein diet hepatic regeneration after partial hepatectomy may be greater than normal in adrenalectomized animals.³⁶ This is not seen in the fasted adrenalectomized animal in which nitrogen for repair must come from the animal's own tissues.³⁷

Observations on the metabolism of fat in the adrenalectomized animal are fragmentary and contradictory in interpretation. It is difficult to fit together the total pattern of fat metabolism under these circumstances. Mention has already been made of the possibility that the conversion of carbohydrate to fat might be accelerated during adrenal insufficiency.³⁰ Neither ketosis nor fatty infiltration in the liver take place in the fasted or stressed adrenalectomized animal as they do in normals.¹⁷ These observations, which have been interpreted in the past to indicate a lowered rate of fat mobilization and catabolism, contrast with the finding that partially starved adrenalectomized rats lose fat more rapidly than intact animals on the same caloric intake,³⁸ and with Welt and Wilhelmi's report³⁰ of increased conversion of carbohydrate to fat without any increase in the fat content of the carcass, both results suggesting that increased fat catabolism occurs after adrenalectomy. Cortisone prevents the fat loss of partially starved adrenalectomized rats. Fully fed adrenalectomized animals have normal fat stores, conceivably compensating for increased fat catabolism by an accelerated conversion of carbohydrate to fat. The absence of ketosis in the face of evidence for increased fat catabolism in the adrenalectomized animals is striking but is consistent with modern concepts of fat metabolism and with the finding of Vilee and Hastings³⁹ that acetate is oxidized to CO₂ at a normal rate in the diaphragms of adrenalectomized rats. This contrasts with the depressed oxidation of acetate and excessive ketone production in diabetes. It is now recognized that acetate, or some comparable 2-carbon fragment, is a normal metabolic product of the catabolism of fatty acids and is an intermediary between fat, carbohydrate and protein metabolism. Acetate, arising from fatty acids, may combine with oxalacetate to enter the Krebs tricarboxylic acid cycle

to yield energy, may be converted to ketone bodies, cholesterol, porphyrins, heme and uric acid or may be used in acetylation reactions. As long as carbohydrate metabolism is proceeding at an adequate rate to supply oxalacetic acid, it would appear that the products of fat catabolism are metabolized preferentially through the Krebs cycle rather than to yield ketone bodies. When carbohydrate utilization is impaired, as in diabetes mellitus, a considerably greater proportion of acetate arising from the catabolism of fat is converted to ketone bodies. It is thus apparent that an accelerated rate of fat catabolism need not necessarily be associated with ketosis, the metabolic fate of acetate being the critical factor in determining the occurrence of ketosis rather than the rate of fat catabolism, as commonly believed in the past. In the absence of the adrenal cortex it would appear that acetate is metabolized predominantly by way of the Krebs cycle so that ketosis does not occur even in the face of enhanced fat catabolism.

In each case in which they have been adequately studied the metabolic abnormalities of the adrenalectomized animal described before have been corrected by the administration of potent adrenal cortical extracts or by C-11 oxygenated cortical steroids. Desoxycorticosterone acetate generally has had no metabolic effects other than those attributable to improving the circulation of adrenal insufficient animals.

METABOLIC EFFECTS OF ADRENAL STEROIDS

Elsewhere in this symposium the nature of the steroids isolated from and presumably secreted by the adrenal cortex has been considered.⁴⁰ Of these only two, desoxycorticosterone and 11-dehydro-17-hydroxycorticosterone (cortisone), have been available in sufficient quantity to allow adequate study. Others, however, have been investigated sufficiently to show that only those compounds with an oxygen on C-11 in the steroid ring have significant actions in intermediary metabolism, but there are indications that the activities of these individual steroids may vary both qualitatively and quantitatively. Desoxycorticosterone is highly active in electrolyte metabolism but relatively impotent in intermediary metabolism. Since comparative data on differential effects of the various C-11 oxygenated steroids are still inadequate and the precise composition of adrenal secretion after ACTH stimulation is not yet clarified, the effects of

ACTH, cortisone and potent adrenal extracts will be considered interchangeably in the discussion to follow. Nevertheless, the possibility should be kept in mind that the metabolic effects of any one injected steroid may be different from that of the normal secretion of the adrenal gland. Again the concept should be emphasized that except when the hormone is used in replacement therapy in adrenalectomized or hypophysectomized animals, any metabolic alteration after hormone injection represents an overdosage effect. The future will tell whether all or only some of these responses reflect exaggerations of physiologic effects.

The basis for our knowledge concerning the role of the adrenal cortex in metabolism was established by the classic report of Long, Katzin and Fry in 1940.¹³ Careful study of this paper emphasizes the importance of this report for it reveals that in the ten years since its publication relatively little new has been added to these original observations. Some of the findings of these investigators in adrenalectomized animals have already been noted. When administered to fasted normal or adrenalectomized animals adrenal extract or C-11 oxygenated cortical steroids were found to induce increases in liver glycogen, blood sugar and nitrogen excretion, without significant alterations in muscle glycogen. It was possible to account for much of the extra carbohydrate by gluconeogenesis from protein. When glucose was fed to animals receiving adrenal extract, large increases in liver glycogen and blood sugar also occurred but there was no change in nitrogen excretion and there was a decrease in the respiratory quotient, without a change in oxygen consumption. With no change in nitrogen excretion to account for the increased liver glycogen these results were interpreted to indicate a decrease in the proportion of calories derived from carbohydrate and an increase in those from fat. A somewhat different interpretation of some of these data may eventually be necessary but, as recorded by Long, these data have been amply confirmed with the use of different steroids and ACTH in every species studied, including man. There is no need at this time to document these confirmatory studies.

The mechanisms by which overdosage with adrenal hormone alters carbohydrate production and utilization remain to be elucidated. In the fasting state much of the extra glycogen comes from endogenous protein. Although it has

been suggested that the adrenal cortex in some way facilitates the conversion of amino acids and other 3-carbon precursors to glycogen,²² there is as yet no convincing evidence for this. Except with massive doses of hormone, amino acid catabolism measured with the aid of N^{15} glycine has been found to be normal.²⁵ The rate of conversion of injected amino acids to urea is likewise normal in the nephrectomized rat treated with adrenal extract.⁴¹ With glucose feeding the amount of glycogen that may be stored in the liver of the animal treated with ACTH or the appropriate cortical steroids may be very great. This is the basis for a useful assay for glycogenic steroids using adrenalectomized mice or rats.⁴² This excessive glycogen storage appears to be due not only to decreased carbohydrate utilization in the body as a whole but also to a specific effect on liver. Chiu and Needham^{43,44} have recently shown that certain adrenal extracts and steroids when added *in vitro* to liver slices increased glycogen production and inhibited glycogen breakdown. Total carbohydrate disappearance was also decreased indicating that the effect was not on glycogen alone. No changes in urea production occurred but there was a small increase in non-protein nitrogen, the composition of which was not established.

Additional evidences for effects of ACTH and adrenal steroids on carbohydrate metabolism beyond those on liver glycogen are found in their anti-insulin and diabetogenic properties. These substances will increase the resistance of fasted normal or adrenalectomized animals to insulin and when given in large doses to the fed normal animal or man may induce hyperglycemia and glycosuria^{45,46} and will accentuate pre-existing diabetes.⁴⁷ In all cases the effects are greater than can be accounted for by gluconeogenesis from protein. The diabetes so induced in rats may be characterized by considerable insulin resistance as measured by the amount of insulin necessary to control glycosuria in contrast with the diabetes of pancreatectomy. Clinical experience with Cushing's syndrome bears this out. However, rapid progression to ketosis and coma is uncommon even without insulin treatment.⁴⁸ The variable occurrence of diabetes in Cushing's syndrome and in patients being treated with ACTH or cortisone may reflect in part the ability of the pancreas to supply sufficient insulin to overcome the diabetogenic effects of these hormones. Patients with pre-existing diabetes respond to small doses

of ACTH and cortisone with hyperglycemia much more readily than non-diabetics.

Information is fragmentary concerning the mechanism of action of adrenal hormone overdosage in modifying carbohydrate metabolism in extrahepatic tissue. That an extrahepatic effect exists is apparent from the report of Ingle et al.⁴⁹ of impaired tolerance to glucose of eviscerated rats treated with adrenal extract and insulin, Li's report of an inhibition of the usual glycogen formation in rat diaphragm *in vitro* in the presence of insulin when animals were pretreated with ACTH,⁵⁰ and in the effects of ACTH and cortisone on the carbohydrate metabolism of the adipose tissue of insulin-treated rats.⁵¹

The fall in the respiratory quotient already noted in animals¹³ and in humans⁵² treated with potent adrenal steroids or ACTH has been interpreted to indicate increased oxidation of fat at the expense of carbohydrate. The finding of fatty livers¹⁷ and of fasting ketosis^{52,53} in normal and diabetic animals⁵⁴ during treatment with these hormones have been taken to support this interpretation. However, this may be an oversimplification. The same fall in respiratory quotient could also result if the conversion of carbohydrate to fat were inhibited or if by some means a net increase in carbohydrate derived from fat could be achieved. While modern biochemical methods have demonstrated that carbon atoms derived from fat may eventually enter carbohydrate molecules, an equal number of carbohydrate molecules have to be oxidized. It is believed, therefore, that a net increase in carbohydrate from fat does not occur under normal circumstances. Nevertheless, evidence has been recently adduced which points to an action of the adrenal cortex on the interconversion of carbohydrate and fat. Welt and Wilhelmi³⁰ find that ACTH will inhibit the uptake of deuterium in the liver and carcass fatty acids of rats fed a fat-free diet and interpret this as evidence for inhibition of liponeogenesis from carbohydrate. Engel and Scott⁵¹ have reported that ACTH or cortisone will increase the accumulation of glycogen in the adipose tissue of insulin-treated rats, a result which can be interpreted to indicate either inhibition of liponeogenesis or stimulation of conversion of fat to carbohydrate in this tissue. Segaloff and Many⁵⁵ recently described marked increases in the urinary excretion of glucose and ketones without appreciable changes in nitrogen excretion in fasted phlorhizinized rats treated with ACTH

or various adrenal steroids. In the face of the pre-existing depleted carbohydrate stores of this preparation and the small change in nitrogen excretion they could account for the glycosuria only by assuming conversion of fat to carbohydrate.

The aforementioned results, which would imply an eventual depletion of fat stores, are difficult to reconcile with the observed relative and absolute increase in the fat content of the carcasses of ACTH-treated rats compared to controls on the same food intake.⁵⁶ The more apparent obesity sometimes seen in patients with Cushing's syndrome or treated with ACTH and in animals treated with certain adrenal steroids is partially explained by the increased food intake of such subjects. It is obvious that a great deal more information is necessary about the relation of the adrenal cortex to fat metabolism.

The mechanism of action of adrenal steroids on nitrogen metabolism has been the subject of much speculation. Almost all recent studies have led to the interpretation that the effect in the fasting organism is exerted predominantly, but not necessarily exclusively, at the level of protein rather than at any intermediary stage of nitrogen metabolism. Thus Hoberman²⁵ reports both a stimulation of protein catabolism and an inhibition of anabolism detected with the use of N^{15} glycine. The latter observation supports the hypothesis first proposed by Albright.⁵⁷ From a series of experiments involving the study of the effect of adrenal hormone on the accumulation of urea and of amino acids in nephrectomized and eviscerated rats, respectively, Engel and Bondy likewise have reached the conclusion that adrenal hormone must act predominantly at the level of whole protein.^{3,31} The results in the eviscerate animals indicate that much of this change in protein metabolism takes place in the extrahepatic tissues. White and Dougherty's studies on lymphoid tissue indicate that the protein of this tissue is peculiarly susceptible to adrenal hormone action.³³ Other tissues showing histologic or other changes indicative of inhibition of growth or of rapid protein breakdown are skin and hair,⁵⁸ bone, bone marrow,⁵⁹ epiphyseal cartilage⁶⁰ and mesenchymal tissue.⁶¹ The over-all effect of adrenal hormone overdosage is inhibition of somatic growth.⁶² This is apparent in the relatively decreased proportion of protein and increased proportion of fat in the carcasses of treated animals. Areas of acceler-

ated growth, such as a healing skin wound or bone fracture, may also be inhibited.^{63,64} The growth-inhibiting effect of adrenal steroids on skin appears to be locally determined since it can be produced by topical application of hormone to the skin.^{65,66}

The magnitude of protein catabolic response to a given dose of adrenal hormone may be considerably modified by dietary and other factors. Thus the intravenous injection of glucose or amino acids may completely abolish the usual increase in urea formation in nephrectomized rats treated with adrenal extract while an intravenous fat emulsion or serum albumin has no effect.⁴¹ Glucose will also suppress the accelerated elevation in plasma amino acids induced by adrenal extract in eviscerate rats.³¹ ACTH stimulates a greater negative nitrogen balance in rats on high fat diets than in those on high carbohydrate or high protein diets.⁶⁷ Conversely, certain non-specific stresses, such as insulin hypoglycemia or formalin injection, may greatly increase the effect of a given dose of hormone on nitrogen metabolism.³ These findings have a bearing on the very variable effects of ACTH and cortisone therapy on nitrogen balance in healthy and ill subjects ingesting different diets. The possibility exists that the hyperphagia which so frequently accompanies ACTH or cortisone treatment represents a homeostatic response by the body to prevent undue nitrogen loss. Indeed, Pearson and Eliel⁶⁸ have recently reported the occurrence of a positive nitrogen balance in a patient being treated with ACTH who was allowed to satisfy his hunger by almost doubling his diet.

COMPARATIVE EFFECTS OF INJURY AND THE ADRENAL CORTEX IN INTERMEDIARY METABOLISM

A discussion of the role of the adrenal cortex in intermediary metabolism would be incomplete without some mention of the comparable effects of non-specific stress. Negative nitrogen balance, impaired carbohydrate utilization, ketosis and fatty liver, negative potassium balance with hypochloremic, hypokaliemic alkalosis, inhibition of lymphoid tissue growth, and eosinopenia occur after injury as well as adrenal hormone overdosage. At the same time there is an increased urinary excretion of corticoids after injury. This had led to widespread acceptance of the concept that the previously described phenomena during injury are simply reflections

of increased adrenal hormone secretion since these same reactions do not take place in the absence of the adrenal cortex. As emphasized by a number of investigators and especially by Ingle¹⁰ this interpretation is clearly incorrect. The adrenalectomized animal maintained on a constant dose of adrenal extract responds to injury in an essentially normal fashion as regards nitrogen excretion,¹⁰ carbohydrate metabolism¹¹ and the development of fatty liver¹⁷ as well as dissolution of lymphoid tissue.¹⁶ Since the available adrenal hormone remains fixed under these experimental conditions, the observed changes cannot be due to adrenal hormone although the hormone is necessary for them to take place. The negative nitrogen balance following both stress and adrenal hormone overdosage can be readily decreased by supplying adequate carbohydrate or amino acids.³ In the presence of excess adrenal hormone mildly stressful stimuli induce prompt changes in nitrogen metabolism, the same stimuli having no effect in the absence of added hormone. More severe stress stimulates an immediate increase in nitrogen metabolism whereas even massive doses of ACTH intravenously produce only delayed effects.⁶⁹ From these results it would seem that excess adrenal hormone sensitizes the organism to respond to stress and conversely that the metabolic response to stress is not due to the adrenal hormone but that the hormone is necessary for it. If one accepts the interpretation that the metabolic response to stress in the healthy organism reflects a reaction designed to protect the organism from damage, then the role of the adrenal cortex in sensitizing the body to react in this fashion becomes more meaningful. Extension of this concept to the other metabolic reactions generally identified with hyperadrenal corticism and stress and to the multitude of other types of defense reactions which are now linked with the adrenal cortex would give some basis for the understanding of the therapeutic significance of and the toxic reactions to ACTH and cortisone. Study of the comparative metabolic effects of stress and adrenal hormone overdosage emphasizes the possibility that many actions that we ordinarily attribute to the adrenal hormone may in reality be induced by other stimuli, the hormone simply facilitating these reactions. Some of the seemingly diverse and contradictory clinical observations with ACTH, such as the apparent promotion of healing in recent and old burns⁷⁰ as contrasted with the usual in-

hibition of wound healing by ACTH, may be explained by future investigation of these relationships.

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Cortisone and ACTH*

A Review of Certain Physiologic Effects and Their Clinical Implications

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THE physiologic and clinical effects of cortisone† and pituitary adrenocorticotrophic hormone (ACTH) are broader in scope than those of any other hormonal agents heretofore employed in clinical medicine. Present understanding of their action has hardly progressed beyond the stage of superficial description. Neither the finer details of the mechanisms involved in their multifarious effects nor the limits of their usefulness and hazards in clinical medicine have yet been defined.

It would be presumptuous for any one individual to pose as an expert in all the areas of physiology, biochemistry and clinical medicine which cortisone and ACTH embrace. Therefore, the review of the present status of these agents which follows is offered with the knowledge that it is not as comprehensive and critical in character as might be desired. An effort will be made, whenever possible, to relate basic physiologic observations to the use of these hormones in clinical medicine. It seems fitting, at this stage of the development of knowledge of these agents, that the physiologic aspects should receive the greatest emphasis. However, not all physiologic effects which have been reported in the literature will be described. The following fields of activity of cortisone and ACTH have been chosen for discussion: (1) organic metabolism, (2) electrolyte metabolism, (3) mesenchymal tissue, (4) lymphoid tissue, blood lymphocytes and eosinophils, (5) allergy and hypersensitivity, (6) infections, bacterial allergic reactions and other inflammatory reactions, (7) the endocrine glands, (8) cardiovascular system, (9) gastrointestinal system and (10) nervous system.

† No distinction will be made in this paper between cortisone and cortisone acetate since their biological activity is essentially the same.

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At the outset it should be emphasized that certain physiologic effects observed in animals and patients have resulted from administration of larger doses than are commonly employed in treatment. Such effects can be regarded as *potential* effects which are not likely to occur with restricted dosage, but which, nevertheless, should be borne in mind when the hormones are used therapeutically.

Since there is such a broad area of overlapping of the effects of cortisone and ACTH, no special effort will be made to consider them separately except in situations in which unmistakable differences exist.

ORGANIC METABOLISM

Carbohydrate Metabolism

For a long time there has been reason to think that administration of compound E (now known as cortisone) or ACTH to man might cause some degree of impairment of carbohydrate tolerance in some cases. Ingle¹ demonstrated in 1941 that cortisone is capable of inducing hyperglycemia and glycosuria in force-fed rats. Five years later, Ingle, Li and Evans² showed that ACTH was capable of inducing similar changes in the rat. This observation suggested that the adrenal cortex of the rat is capable of responding to stimulation by ACTH with the production of large amounts of cortisone-like steroid hormones. Long, Katzin and Fry³ observed that the glycosuria of partially depancreatized rats could be greatly augmented by administration of cortisone. More recently, Kobernick and More⁴ observed the development of a diabetic state associated with lipemia and hydropic changes in the islet cells of rabbits during administration of 20 mg. of cortisone acetate daily.

Patients with Cushing's syndrome frequently

exhibit impaired carbohydrate tolerance, which is apparently directly related to overproduction of carbohydrate-active adrenal steroids by hyperfunctioning adrenal cortices.⁵ It also has been noted that cortisone lessens the sensitivity to insulin of patients suffering from Addison's disease, maintains the blood sugar of such patients during prolonged fasting and greatly intensifies hyperglycemia, glycosuria and ketonuria of patients who have coexisting Addison's disease and diabetes mellitus.⁵

The doses of cortisone and ACTH used therapeutically in man have been relatively small, on basis of body weight, compared to the amounts which Ingle and associates^{1,2} found necessary for induction of frank diabetes in rats. Possibly because of this, alterations in carbohydrate metabolism, if they occur at all, have usually not been pronounced in patients with intact adrenal glands and pancreas who have received cortisone or ACTH for therapeutic purposes. There have been a few instances, however, in which cortisone or ACTH had rather pronounced diabetogenic effects. For example, Pearson and Eliel⁶ observed the development of a severe diabetic state associated with ketosis in a young man on administration of large doses of cortisone and ACTH as treatment for acute leukemia. Conn, Louis and Wheeler⁷ induced a temporary diabetic state in three normal adults by administration of 120 to 150 mg. of ACTH daily for eight to ten consecutive days. However, observations like the foregoing are the exception rather than the rule, for the majority of patients treated with cortisone or ACTH have not exhibited clinically significant impairment of carbohydrate tolerance.

Intensification of Pre-existing Diabetes. It would be anticipated that cortisone or ACTH might intensify pre-existing diabetes. This has proved to be the case. This effect is most readily observed when cortisone is administered to patients with coexisting Addison's disease and diabetes mellitus, as in the cases reported by Sprague and associates.⁸ However, it has been observed also in diabetic patients to whom cortisone or ACTH has been administered in the treatment of other conditions. Boland and Headley⁹ reported the case of a patient with rheumatoid arthritis and diabetes, whose daily requirement for insulin increased from 10 to 50 units daily during administration of cortisone. Three days after withdrawal of cortisone the insulin requirement dropped to 10 units daily. Brown and

associates¹⁰ likewise observed intensification of diabetes following administration of cortisone or ACTH to diabetic patients with coexisting rheumatoid arthritis. In these cases the characteristic effects of cortisone and ACTH on the rheumatoid arthritis occurred irrespective of whether the metabolic manifestations of diabetes were permitted to intensify or were controlled by additional amounts of insulin. Perera and associates¹¹ noted an increase in fasting blood sugar and total urinary reducing substances during administration of cortisone in a case of hypertension and diabetes.

The more pronounced diabetogenic effects of the hormones in cases of diabetes or coexisting Addison's disease and diabetes suggest that a deficient insulin producing mechanism might play a role in the production of hyperglycemia and glycosuria by these agents. In support of this Forsham and associates¹² have reported a series of studies of the effects of cortisone and ACTH on carbohydrate metabolism of patients with Cushing's syndrome, Addison's disease and Addison's disease coexisting with diabetes. They pointed out that patients with intact adrenal glands and pancreas, when treated with ACTH for periods of two weeks or more, showed evidences of diabetes infrequently. Likewise, the administration of a single 25 mg. dose of ACTH to five patients with adrenal hyperplasia led to only slight increases in the level of the blood sugar. In contrast, this amount of ACTH administered to twelve diabetic patients produced marked rises in the level of the blood sugar. Similarly, in patients with Addison's disease, the administration of 100 mg. of cortisone led to only slight elevation of the blood sugar, whereas in patients with coexisting Addison's disease and diabetes, the administration of as little as 5 mg. of cortisone per day induced marked glycosuria. The authors felt that the large functional reserve of the islet tissue in the majority of patients who have received ACTH or cortisone for therapeutic purposes is responsible for the infrequent development of significant impairment of carbohydrate tolerance. In this connection it is perhaps pertinent that Sprague and associates¹³ noted that two of four patients who exhibited impairment of carbohydrate tolerance under the influence of cortisone had diabetes in their families.

Renal Glycosuria. That the glycosuria which may be induced in human subjects by administration of ACTH or cortisone may be related, in

part, to lowering of the renal threshold for glucose was suggested by the observations of Conn, Louis and Wheeler.⁷ They noted that the glycosuria which developed during administration of ACTH was sometimes associated with only minor elevation of the blood sugar. Kass, Ingbar and Finland¹⁴ have made similar observations on patients treated with cortisone, and McEwen¹⁵ observed pronounced glycosuria associated with mild hyperglycemia during administration of cortisone in the case of a girl, ten years old, who had Still's disease.

Clinical Implications. The effects of cortisone and ACTH on carbohydrate tolerance persist only as long as the hormone in question is being administered or for a short time thereafter. Fears that these agents may induce a permanent state of diabetes are apparently unfounded. In clinical practice it is clearly wise to test the urine of both diabetic and non-diabetic patients for sugar at intervals during administration of cortisone or ACTH and to carry out appropriate investigations and treatment if glycosuria occurs. Particular caution is necessary for diabetic patients. However, the presence of diabetes hardly constitutes a contraindication to the therapeutic use of cortisone and ACTH for conditions which might be benefited by them.

Among patients with Addison's disease, the carbohydrate activity of cortisone has beneficial effects in preventing hypoglycemia during fasting and probably also in other more subtle ways. In the experience of the reviewer cortisone is of great value in the treatment of patients with coexisting Addison's disease and diabetes mellitus although the diabetes may be greatly intensified.

Nitrogen Metabolism and Growth

Some of the most profound effects of large doses of cortisone and ACTH are those which are reflected in alterations in the nitrogenous constituents of the body. Probably such alterations are closely related to the effects of these agents on growth and possibly to their effects on a variety of diseases involving mesenchymal tissue.

Nitrogen Balance. It has been observed repeatedly in patients with a variety of clinical conditions that administration of cortisone and ACTH in relatively large dosage may give rise to increases in urinary nitrogen with the development of negative nitrogen balance. For example, Thorn and associates¹⁶ observed a

58 per cent increase in urinary nitrogen in a case of pituitary insufficiency during administration of 40 mg. of ACTH daily for six days. Bartter and co-workers¹⁷ made similar observations in three patients with panhypopituitarism. Conn, Louis and Wheeler⁷ observed it in three normal adults during administration of 120 to 150 mg. of ACTH daily for eight to ten consecutive days. Pearson and associates¹⁸ observed that both ACTH and cortisone in large doses induced profound losses of nitrogen in patients with lymphoid tumors. They made the important observation that doubling of the diet, including its content of protein, resulted in an abrupt shift from a negative to a positive nitrogen balance. Sprague and associates¹³ induced negative nitrogen balances in patients afflicted with rheumatoid arthritis with daily doses of 200 mg. of cortisone acetate or 100 mg. of ACTH. Thorn and associates¹⁶ have made the reasonable suggestion that the loss of nitrogen which may occur when ACTH is administered is one manifestation of excessive production of cortisone-like steroid hormones by the adrenal cortices.

In the early experiments of Ingle and associates¹⁹ on the induction of diabetes in rats by cortisone or ACTH, it was observed that a constant accompaniment of the diabetic state was a pronounced increase in urinary nitrogen. However, it was noted that the organism apparently possesses some ability to adapt itself to the catabolic effects of these hormones, as the peak of nitrogen loss was not sustained during continued administration of the hormones.

Sprague and associates¹³ have noted that the loss of nitrogen which ordinarily followed administration of large doses of cortisone to a patient with rheumatoid arthritis could be prevented by simultaneous administration of testosterone propionate. This observation is reminiscent of Albright's²⁰ previous demonstration that testosterone induced retention of nitrogen in patients with Cushing's syndrome. Pearson and Eliel²¹ have presented evidence suggesting that testosterone administered simultaneously with ACTH or cortisone to patients with lymphoid tumors abolishes catabolism of muscle tissue but does not interfere with catabolism of lymphoid tissue. Whitney and Bennett²² have made the interesting observation that the catabolic effect of ACTH on protein in rats may be inhibited in part simply by increasing the intake of potassium.

Growth. There is convincing evidence, which

has been reviewed by Ingle,²³ that cortisone is capable of inhibiting growth, probably as a consequence of its catabolic or antianabolic effects on protein. The effects of cortisone and ACTH on growth of neoplastic tissue are most marked in the case of lymphoid tumors and less marked in the case of neoplasms derived from epithelial or mesenchymal tissues.

Plasma Proteins. Cortisone and ACTH are capable of correcting the abnormal concentrations of plasma proteins, particularly the globulin fraction, which characterize some cases of rheumatoid arthritis and other diseases of mesenchymal tissue. Elevated values of serum globulin and depressed values of serum albumin frequently change to normal during administration of cortisone or ACTH. This was reported in the initial paper of Hench and associates²⁴ on the effects of cortisone and ACTH in rheumatoid arthritis and also has been reported by numerous others in a variety of diseases associated with abnormalities of the serum proteins. Sprague and associates¹³ also reported that zinc sulphate turbidity, which presumably is a rough measure of serum gamma globulin, decreased significantly during administration of cortisone. Bongiovanni and co-workers²⁵ noted that administration of ACTH to patients with various types of cirrhosis of the liver resulted in a fall in concentration of gamma globulin, a rise in that of albumin and a fall in the total protein. They concluded that ACTH is capable of improving albumin synthesis by the liver in some types of cirrhosis. In young adult male rats, Winter, Silber and Stoerk²⁶ found that the concentration of serum alpha globulin was decreased but that of gamma globulin was increased during administration of cortisone.

Uric Acid Metabolism. Both cortisone and ACTH have been observed to cause an increase in urinary uric acid in a variety of conditions. This phenomenon was noted in 1947 by Thorn, Prunty and Forsham¹⁶ in a man with pituitary insufficiency during administration of ACTH and has since been observed in a variety of other conditions, including gout, during administration of cortisone or ACTH.

Benedict and associates²⁷ have estimated the size of the miscible pool of uric acid by injecting isotopic uric acid into a gouty and a normal subject and measuring the dilution of the isotopic compound. In a patient with gout the miscible pool of uric acid was about 31 gm. or approximately thirty times normal. It fell to

about 2 gm. or approximately twice normal when uricosuric doses of aspirin were given. ACTH in both gouty and normal subjects caused uricosuria, which was apparently due to increased renal clearance of uric acid.

Conn and associates^{7,28} have emphasized the close temporal relationship between increase in urinary uric acid during administration of ACTH to normal subjects and the appearance of a temporary state of diabetes.

Amino Acids. Studies of the effects of cortisone and ACTH on the metabolism of various amino acids are still relatively few in number. Clark²⁹ employed isotopic glycine as a means of studying the effects of cortisone on protein metabolism in the rat; he used the excretion of the isotope as a measure of the amount of nitrogen being used for synthesis of protein. In animals receiving cortisone the synthesis of protein was decreased compared to that of the control animals. This observation lends support to the belief of Albright²⁰ that the effects of cortisone-like steroids are antianabolic rather than catabolic.

A study by Umbreit and Tonhazy³⁰ on the effect of cortisone on proline oxidation in homogenates of rat kidney represents an attempt to localize a site of biochemical action of cortisone. These investigators found that adrenalectomy was followed by a marked decrease of proline oxidation. Treatment with cortisone, however, maintained the activity of the proline oxidizing system, or even restored it to normal. Since proline was oxidized to completion via glutamate and since neither adrenalectomy nor treatment with cortisone markedly affected the ability of kidney homogenates to oxidize glutamate or other compounds of the cycle, it appeared that the effects of cortisone were exerted at the level of the proline oxidizing enzyme. The extent to which this observation applies to the action of cortisone on other tissues remains to be determined.

Holbrook and associates³¹ have observed a marked rise in urinary excretion of several amino acids during each remission of rheumatoid arthritis, whether occurring spontaneously or induced by cortisone, ACTH, pregnancy or jaundice. Stephens and associates³² noted a striking increase of apparently free histidine in urine, determined by microbiologic assay, of five patients with rheumatoid arthritis during treatment with cortisone and of ten during treatment with ACTH. To date an increase in

urinary excretion of histidine by patients with rheumatoid arthritis has been observed by these investigators only in association with clinical remission. The significance of this observation is unknown.

Clinical Implications. Fortunately, doses of cortisone and ACTH which are now being employed for therapeutic purposes probably do not frequently cause pronounced acceleration of the catabolism of protein. Nevertheless, the effects of the hormones on protein metabolism may be related to their inhibition of hair growth and tumor growth, to the development of cutaneous striae and to delayed healing of wounds.

Since large doses are necessary in the treatment of some conditions, it is desirable that ways be found of inhibiting undesirable catabolic effects while preserving therapeutic effects. Reference has already been made to the simple expedient of increasing dietary intake as a means of circumventing catabolic effects as described by Pearson and associates.¹⁸ The concurrent use of testosterone has similar effects¹³ although simultaneous administration of cortisone and testosterone does not prevent the latter from exerting its usual androgenic effects in women. The suggestion of Whitney and Bennett²² that the catabolic effects of ACTH may be lessened by increasing the intake of potassium is deserving of further clinical investigation.

The effects of cortisone and ACTH on uric acid metabolism are proving to be of some use in the clinical management of acute gouty arthritis, but the ultimate place of these agents in the treatment of gout remains to be determined. It has been observed that ACTH is capable of both terminating and inducing attacks of acute gouty arthritis. Gutman and Yü³³ have emphasized that available evidence does not justify the view that the pituitary or the adrenal glands or both play a prominent role in the pathogenesis of gout.

Fat Metabolism

While there is ample evidence that the adrenal cortex is involved in the metabolism of fat, relatively little is known concerning the physiologic processes involved, particularly in man. The subject has been reviewed by Ingle,³⁴ by Wertheimer and Shapiro³⁵ and by Hartman and Brownell.³⁶

Ketonuria. Ingle and Thorn³⁷ noted that

exacerbation of the diabetes of partially depancreatized and partially depancreatized and adrenalectomized rats by administration of cortisone was associated with an increased excretion of ketone bodies in the urine. A similar observation was made by Sprague and associates⁸ on patients with coexisting Addison's disease and diabetes mellitus. It also has been noted that the characteristic ketonuria of phlorhizinized rats diminishes after adrenalectomy, but can be restored by administration of cortisone.³⁸⁻⁴⁰ It is apparent that such observations do not necessarily imply a direct participation of cortisone in metabolism of fat, since the observed ketonuria may simply be a secondary manifestation of intensified diabetes consequent to administration of the hormone.

Transient ketonuria was observed by Perera and associates¹¹ in some non-diabetic patients during administration of 80 mg. of cortisone daily. Thorn and associates⁴¹ reported a transient increase in ketones in the blood of five of six patients who had Addison's disease during administration of cortisone.

Blood Lipids. Kobernick and More⁴ observed that cortisone acetate induced temporary diabetes associated with an increase in blood lipids in rabbits. Likewise, Katzin and Goldman⁴² noted grossly lipemic serum in rabbits during administration of cortisone acetate. Whether the observed hyperlipemia represented a direct effect of cortisone, or was secondary to an induced diabetic state, or whether both factors were involved, was not clear.

In human subjects, certain evidence suggests that under some circumstances, ACTH and cortisone may exert opposite effects on the concentration of serum cholesterol. Conn and his associates⁴³ observed a marked decrease in total serum cholesterol of normal subjects, due chiefly to decrease in the ester fraction, after several days of administration of 39 to 100 mg. of ACTH daily. A similar but more pronounced effect was observed in the case of a patient with Cushing's syndrome who received 100 mg. of ACTH daily. As might be expected, the serum cholesterol of two patients with Addison's disease did not decrease in response to ACTH. Conn and his associates⁴³ considered it probable that the serum cholesterol, particularly the ester fraction, constitutes a source of material for synthesis of adrenal cortical hormones after the adrenal cortex has been depleted of its reserve supply of cholesterol during stimulation by ACTH.

Cortisone, on the other hand, has now been reported by several observers to cause a rise in total serum cholesterol in some cases. For example, Adlersberg, Schaefer and Drachman⁴⁴ reported that there was frequently an increase in total serum cholesterol with a concomitant rise in esterified cholesterol and phospholipids during administration of cortisone. In apparent contradiction of the observations of Conn and associates,⁴³ the same events were observed during prolonged administration of ACTH. However, the discrepancy may be due to the fact that the experiments of Conn and associates⁴³ lasted only a few days while those of Adlersberg and associates⁴⁴ involved more prolonged administration of ACTH. That cortisone does not always induce a rise in serum cholesterol is suggested by the observations of Perera and associates¹¹ and O'Connell and Burns⁴⁵ who noted a fall in serum cholesterol during treatment with cortisone.

That the increase in serum cholesterol observed in some patients during treatment with cortisone or ACTH might be in part a manifestation of depression of thyroid function is suggested by the work of Wolfson and associates.⁴⁶ They and others have noted other evidences of depression of thyroid function in such patients during administration of cortisone or ACTH, including decrease in basal metabolic rate, decrease in plasma protein bound iodine and diminished uptake of radioactive iodine.

Liver Fat. The finding of a fatty liver at necropsy in cases of Cushing's syndrome is not uncommon. Gorsuch⁴⁷ found reports of fatty livers in twenty-six of forty-eight cases in which data were available. Likewise, Baker and associates⁴⁸ observed fatty livers in rats treated with ACTH. As yet, however, no instance has come to the attention of the reviewer in which a fatty liver in a human being could be attributed with certainty to administration of cortisone or ACTH.

Body Fat. The characteristic alterations in the body fat of patients suffering from spontaneous Cushing's syndrome suggest that cortisone and allied hormones might exert an influence on deposition of fat. Changes in body fat similar to those observed in spontaneous Cushing's syndrome may occur among patients in whom an excess of adrenal hormones is maintained for long periods by administration of cortisone or ACTH. This suggestion is supported by a number of experimental and clinical observations.

Winter, Silber and Stoerk²⁶ observed that protracted administration of cortisone acetate to rats resulted in a relative increase in depot fat. Stoerk and Porter⁴⁹ reported that the rate of loss of body fat of untreated adrenalectomized rats during starvation for five days was markedly retarded by administration of 2 mg. of cortisone acetate daily, although the total loss of weight was much greater in the rats which received cortisone than in untreated control animals. Likewise, in rats that were fasted prior to adrenalectomy and then were permitted to eat, cortisone decreased the rate of gain of weight but accelerated the rate of deposition of fat. On the contrary, Antopol⁵⁰ observed a decrease in body fat and in the size of the hibernating fat bodies of normal mice during administration of large doses of cortisone.

Baker, Ingle and Li⁵¹ made the interesting observation that in rats treated with ACTH, the brown fat of the interscapular (hibernating) gland took on somewhat the appearance of white adipose tissue. Histochemical studies revealed an increase in the glyceride content of brown adipose tissue. It was noted, however, that treatment of hypophysectomized rats with three times the amount of ACTH used to induce the foregoing changes in intact rats failed to maintain the fat content of the interscapular gland; this suggests that some other pituitary factor than ACTH may be involved. Similar observations have apparently not been made in rats treated with cortisone. Ingle⁵² has suggested the interesting possibility that the observed effects of ACTH on the interscapular glands of rats might have some bearing on the mechanism of development of the fatty cervicodorsal hump in patients with spontaneous Cushing's syndrome.

Clinical Implications. At present it cannot be said that the effects of cortisone and ACTH on fat metabolism have important clinical implications. Pronounced alterations in the distribution of body fat are limited for the most part to patients receiving large doses of the hormones for prolonged periods. Adlersberg and associates⁴⁴ have speculated that the hypercholesterolemia induced by cortisone and ACTH may be relevant to the pathogenesis of arteriosclerosis in patients with spontaneous Cushing's syndrome. However, prolonged observation of many patients will be necessary before any conclusions can be reached concerning the possible induction of arteriosclerosis by exogenous cortisone or ACTH.

ELECTROLYTE METABOLISM

While the action of cortisone and ACTH on electrolyte metabolism apparently has no relationship to the therapeutic effects of these agents in diseases which are not characterized by adrenal cortical insufficiency, nevertheless their capacity to induce retention of sodium chloride and water and loss of potassium requires careful consideration in their clinical use.

Sodium Chloride. The early studies of Thorn, Engel and Lewis⁵³ on the dog and rat in which single doses of cortisone were employed, suggested that it and related hormones might cause an increased excretion of sodium and chloride. It was hypothesized that the 11,17-oxygenated steroids served to counterbalance the salt-retaining activity of desoxycorticosterone, and that the maintenance of the equilibrium of sodium chloride depended on a balance between the effects of the two types of adrenal cortical hormone.

Some clarification of the situation came when Ingle and associates⁵⁴ in experiments on rats showed that the increased excretion of salt due to cortisone was of short duration (one to three days) and that a normal balance was quickly restored. Sprague and associates⁵⁵ made similar observations in the case of a patient with Addison's disease who received 20 mg. of natural cortisone daily for nine days. More recent evidence indicates that the effects of cortisone on sodium and chloride balance in man are variable, depending on dosage, duration of administration, possibly on the functional state on the subject's own adrenal cortices, and perhaps on other factors which have not yet been elucidated.

The relatively poor ability of cortisone, as compared to desoxycorticosterone acetate, to maintain life in the adrenalectomized animal may be related in part to weak electrolyte activity. In any event, the patient with Addison's disease and the adrenalectomized animal provide good subjects for the study of the electrolyte effects of the hormone independent of endogenous adrenal hormones. As a result of a study of the excretion of sodium by patients with Addison's disease, Thorn and associates⁴¹ concluded that cortisone is approximately one-fiftieth as effective as desoxycorticosterone acetate in causing retention of sodium. Sprague and associates⁵⁶ observed virtually no effect of 100 mg. and 50 mg. of cortisone acetate daily

on two patients with Addison's disease who were being maintained with desoxycorticosterone acetate. On the other hand, Perera and associates¹¹ observed retention of sodium when 80 mg. of cortisone acetate was administered daily to a patient with Addison's disease who was already receiving 2 mg. of desoxycorticosterone acetate and 8 gm. of sodium chloride daily. In a somewhat more extensive study of the effects of cortisone acetate on electrolyte balance of two patients with Addison's disease, Salassa and associates⁵⁷ found that 50 mg. of the hormone daily, in the absence of desoxycorticosterone acetate, did not have sufficient salt-retaining activity to prevent progressive dehydration due to loss of sodium chloride. A more rapid loss of sodium chloride occurred when all treatment was withdrawn. The conclusion seems justified that cortisone acetate, by itself, in the absence of the adrenals, has only weak salt-retaining properties.

In a variety of subjects with intact adrenals, cortisone acetate has frequently been observed to cause retention of sodium chloride and water, sometimes with the development of edema. In some instances, it has been noted that retention occurred early in the period of administration of the hormone, but that more prolonged administration was associated with increased excretion of sodium, chloride and water and subsidence of edema.¹³

Most observers agree that ACTH may induce at least a temporary retention of sodium and chloride in both rats and man with intact adrenals. Ingle, Li and Evans² demonstrated this in normal rats in 1946. Mason and associates⁵⁸ and Forsham and associates⁵⁹ observed this effect in human subjects before the present era of clinical application of ACTH, and the observation has been confirmed more recently on numerous occasions. Forsham and associates⁵⁹ interpreted the observation as evidence of hypersecretion of desoxycorticosterone-like hormones by the stimulated adrenal cortices. Retention of salt and water under the influence of ACTH has now been reported in cases of pituitary insufficiency,^{16,17,60,61} rheumatoid arthritis,^{13,62-66} Cushing's syndrome,⁶⁷ chronic lymphatic leukemia,⁶⁸ disseminated lupus erythematosus⁶⁹⁻⁷¹ acute rheumatic fever⁶⁶ and in a variety of other conditions.

As in the case of cortisone, the retention of sodium chloride which is induced by ACTH may not persist throughout a prolonged period

of administration of the hormone. This phenomenon is illustrated by the balance studies of Sprague and associates,¹³ who observed prompt and marked retention of sodium and chloride during the first few days of administration of ACTH, followed by increased excretion so that the balances became negative while the hormone was still being administered.

Various effects of ACTH on excretion of sodium chloride and water in the nephrotic syndrome have been reported. Farnsworth⁷² observed profound diuresis in eight patients; with one exception it occurred after withdrawal of ACTH. Barnett and associates⁷³ observed that the administration of ACTH for seven to twelve days induced rapid and sustained diuresis in eight children with the nephrotic syndrome. Two additional children had no diuresis. Riley⁷⁴ studied fourteen children with nephrotic edema and observed a rapid and complete clearance of the edema in five; however, all five had relapses. In four of these the relapses responded to a second period of administration of ACTH. An additional four patients had definite diuresis after ACTH but their edema did not clear completely. Thorn and associates⁷⁵ speculated that the diuresis of sodium and water in patients with the nephrotic syndrome during and after administration of ACTH is accounted for by three mechanisms: (1) renal "tubular fatigue" consequent to a high level of 11, 17-oxygenated steroids, or competitive inhibition by the latter compounds of the effects of 11-desoxy-like steroids or both; (2) increased glomerular filtration during ACTH therapy and (3) the enhancement of these effects by temporary adrenal cortical insufficiency following withdrawal of ACTH or cortisone.

Potassium. Both cortisone and ACTH have been observed to cause an increased excretion of potassium in a variety of clinical conditions in which balance studies have been made. Sprague and associates¹³ have pointed out that the metabolic data in their cases indicated that the increased amount of potassium in the urine was derived from both intracellular and extracellular fluids. The portion which came from intracellular fluid was regarded as one manifestation of protein catabolism, since it was accompanied by an increased excretion of nitrogen. When cortisone acetate and testosterone propionate were administered simultaneously to one patient, loss of nitrogen was prevented, but there was still a small loss of potassium which could be explained

by an observed decrease in the concentration of potassium in the extracellular fluid as measured in blood plasma.⁷⁶

Plasma Electrolytes. Both cortisone and ACTH have been observed to induce hypochloremic, hypopotassemic alkalosis, similar in all respects to that observed in spontaneous Cushing's syndrome. As a rule, relatively large doses of the hormones have been necessary for the induction of alkalosis. Sprague and associates⁷⁷ observed this type of alkalosis in a case of spontaneous Cushing's syndrome in which compound F was isolated from the urine. It was presumed that the alkalosis in this case was a consequence of excessive secretion of compound F by hyperfunctioning adrenal cortices. A similar type of alkalosis has been described by Eliel, Pearson and Rawson⁷⁸ in patients undergoing the stress of major surgical procedures, but the precise role of the adrenal cortices in the production of alkalosis under these circumstances is not established with certainty. The occurrence of alkalosis in a patient with rheumatoid arthritis during administration of 200 mg. of cortisone acetate daily, when loss of intracellular potassium was presumably prevented by concomitant administration of testosterone propionate, suggests that depletion of intracellular potassium is not a necessary condition for the development of this type of alkalosis.¹⁸

Clinical Implications. In some clinical circumstances, such as the presence of impaired myocardial function or severe hypertension, retention of salt and water during administration of cortisone or ACTH may impose a hazard on the patient. Potassium depletion may be associated with weakness of skeletal muscles and myocardium. When administration of large doses of cortisone or ACTH is necessary, restriction of the intake of sodium chloride and administration of potassium salts may circumvent complications due to the electrolyte effects of the hormones.

EFFECTS ON MESENCHYMAL TISSUE

Certain of the derivatives of the primitive mesenchyme, including connective tissue, synovia, reticulum, vascular tissue and muscle, are prominently involved in the so-called collagen diseases. Inflammation of these tissues is strikingly modified by exogenous cortisone and ACTH, with corresponding improvement in the clinical manifestations of the disease in question. An understanding of the mechanism of action

of cortisone and ACTH on mesenchymal tissues would help to explain the therapeutic effects of the hormones on the collagen diseases. Unfortunately, present day knowledge contributes little to such an understanding.

Reaction of Tissues to Injury. Administration of cortisone or ACTH inhibits the reactivity of mesenchymal tissue to a variety of injurious substances. These include turpentine injected into white rats,⁷⁹ talc placed in the peritoneal cavity of rats,⁸⁰ formaldehyde injected into the vicinity of joints of rats,⁸¹ and a number of different bacteria and bacterial products which will be discussed later.

Wound Healing and Vascularization. Wounds are another type of injury to mesenchymal tissues to which reaction is inhibited by an excess of adrenal hormones. Poor healing of wounds is a common accompaniment of spontaneous Cushing's syndrome, a condition characterized by a chronic excess of cortisone-like hormones. Effects of cortisone, ACTH and allied substances on healing of wounds in mice have been reported by Spain, Molomut and Haber;⁸² in rats, by Baker and Whitaker;⁸³ in rabbits, by Ragan and associates,⁸⁴ by Creditor and associates,⁸⁵ by Plotz and associates⁸⁶ and by Stinchfield;⁸⁷ in man, by Plotz, Blunt and Ragan,⁸⁸ by Behrman and Goodman,⁸⁹ by Videbaek and associates⁹⁰ and by Creditor and associates.⁸⁵ While their observations differ in certain details, they are in essential agreement that the hormones are capable of inhibiting the healing of wounds, as evidenced by interference with the formation of granulation tissue, fibroblasts and ground substance, impaired phagocytosis and delayed vascularization.

The biochemical details of the observed inhibition of wound healing have not been elucidated. Videbaek and associates⁹⁰ noted a disappearance of hyaluronic acid from connective tissue of wounds of patients with acute rheumatic fever during treatment with cortisone or ACTH. Creditor and associates⁸⁵ found that irrigation of wounds in one patient and in rabbits with hyaluronidase failed to restore normal healing properties during administration of ACTH. Ragan and associates⁸⁴ made the reasonable suggestion that the catabolic or antianabolic effects of the hormones on mesenchymal tissue might be responsible for the observed defects in the healing process, as well as for suppression of the activity of mesenchymal tissue (synovia) in rheumatoid arthritis. In the latter connection

it is of interest that Sprague and associates⁷⁶ noted no inhibition of antirheumatic activity of cortisone by concomitant administration of testosterone in a dose sufficient to maintain nitrogen balance in a patient who had rheumatoid arthritis.

Synovia in Rheumatoid Arthritis. In the initial report of Hench and co-workers²⁴ the effects of cortisone on the histopathologic changes in the synovial membrane in one case of rheumatoid arthritis were described. A specimen of synovial membrane removed from a knee forty-three days after injection of cortisone was begun, although not normal, showed definite histologic evidence of healing and less inflammation than was present in a specimen removed from the same knee before cortisone was administered. This observation was subsequently confirmed by others. In a later report Hench and co-workers⁶² gave the results of biopsy of synovial membrane of the knee in seven cases before and at various times during the use of cortisone or ACTH or both. In each instance there was histologic improvement as indicated by a decreased number of plasma cells and lymphocytes, reduction of papillary tufting, reduction or absence of deposition of fibrin and lessened necrosis and edema.

Clark, Ropes and Bauer⁹¹ observed a marked decrease in the cell count of the synovial fluid, a rise in the viscosity and a return of the lowered concentration of sugar to normal in one case of rheumatoid arthritis as a result of treatment with ACTH. It was further noted that the mucin precipitated normally, indicating a return of the synovial mucin polysaccharide to normal. Conn⁹² reported a similar observation by his associate Robinson. He suggested that the ability of the rheumatoid arthritic to make a longer chain polysaccharide may be a fundamental point in the mechanism of action of ACTH and cortisone in rheumatoid arthritis.

Hollander, Stoner and Brown⁹³ employed measurements of intra-articular temperatures as a means of studying the effects of cortisone and ACTH on the synovia in rheumatoid arthritis. In every case studied the temperature fell at least 1.5°C. within the first twenty-four hours after the administration of 300 mg. of cortisone acetate and within four hours after the administration of 25 mg. of ACTH. Continued administration of either hormone produced a further fall in articular temperatures to approximately normal levels.

Steck and associates⁹⁴ observed a marked lowering of increased electrical potential between knee joint cavity and skin during the first hour after intramuscular administration of 25 mg. of ACTH to six patients with rheumatoid arthritis.

Comment. It is apparent that cortisone and ACTH inhibit the reactivity or hyperreactivity of mesenchymal tissue to a wide variety of noxious agents. Likewise, these hormones modify the clinical course of a group of diseases of mesenchymal tissue with different clinical manifestations and perhaps different causative agents. One is thus led to certain speculations. It would appear that the effects of cortisone and ACTH on the reactivity of mesenchymal tissue must be exerted at some fundamental biochemical level which is common to a variety of animal species and to a variety of injurious agents. The agent which initiates mesenchymal reactivity is not itself affected; rather, it is the reactivity of the tissue that is depressed so that the noxious agent, whatever it may be, cannot exert its customary ill effects. In the sense that cortisone and ACTH endow the tissue with the ability to block reactivity to many different agents, the effects of the hormones in the collagen diseases must be regarded as non-specific or possibly pharmacodynamic in character.

EFFECTS ON LYMPHOID TISSUE, BLOOD LYMPHOCYTES AND EOSINOPHILS

Among the tissues of the body exhibiting the greatest sensitivity to adrenal cortical hormones are lymphoid tissue, blood lymphocytes and blood eosinophils. It is perhaps pertinent to note that these tissues are descendants of the primitive mesenchyme. The effect of exogenous cortisone and ACTH on these tissues has found a limited therapeutic and diagnostic application in clinical medicine.

Lymphoid Tissue and Lymphocytes in Blood. Administration of cortisone or ACTH in high dosage to rats and mice causes atrophy of the thymus, spleen and lymph nodes and a decrease in the number of lymphocytes in the blood. Investigations in this field have been reviewed by Ingle.²³ The observation of Stoerk and Solotorovsky⁹⁵ that there is no diminution in mitotic activity in the atrophic thymus of rats during administration of cortisone suggests that the loss of tissue is due to accelerated destruction of lymphocytes. Heilman⁹⁶ had previously observed that cortisone caused increased destruc-

tion of small and medium-sized lymphocytes in the migration zone of tissue cultures of lymph nodes. Feldman⁹⁷ observed that cortisone rapidly injured lymphocytes *in vitro*.

The effects of cortisone on lymphoid tissue and lymphocytes in the blood of patients appear to be less pronounced than in animals, possibly owing to the administration of relatively smaller doses of the hormone to patients. Thorn and Forsham⁹⁸ observed only a transitory decrease in the number of lymphocytes in four patients with Addison's disease as a result of administration of 100 mg. of cortisone acetate daily for five days. Sprague and associates¹³ noted no significant change in the average number of lymphocytes during or after protracted administration of cortisone to a group of patients with rheumatoid arthritis and related diseases, although decreases in lymphocytes were observed in individual cases during short periods of administration of the hormone. Furthermore, in the experience of the reviewer, spontaneous Cushing's syndrome is not uniformly associated with lymphocytopenia.

Eosinophils in Blood. Several studies suggest that the eosinophils of the blood are more vulnerable to the effects of cortisone than are the lymphocytes. Thus, Speirs and Meyer⁹⁹ found that doses of cortisone smaller than 1 microgram caused some degree of eosinopenia in the adrenalectomized mouse, while as little as 3 micrograms caused a 96 per cent decrease in the number of circulating eosinophils in four hours.

The effect of cortisone and allied hormones on the eosinophils in the blood was first observed in patients with Addison's disease. Hills, Forsham and Finch¹⁰⁰ found that the intramuscular administration of 20 mg. of compound F to five patients with Addison's disease caused an average decrease of 63 per cent in the number of circulating eosinophils.

Certain evidence suggests that the hematologic effects of cortisone may be less pronounced than those of compound F, but there is need for a systematic comparison of the two compounds. Thorn and Forsham⁹⁸ noted a fall of from 20 to 50 per cent in the number of circulating eosinophils in three of four patients with Addison's disease after administration of 100 mg. of cortisone acetate daily for five days. Intravenous administration of 5 to 50 mg. of cortisone acetate to nine patients with Addison's disease caused a more significant decrease in eosinophils in four

hours. In patients with rheumatoid arthritis and allied diseases, Conn¹⁰¹ noted that the effects of as much as 200 mg. of cortisone acetate daily on circulating eosinophils were delayed, possibly owing to slow absorption of the hormone from the sites of injection. Reynolds¹⁰² observed no significant alteration in the average number of eosinophils of a group of patients with rheumatoid arthritis and allied diseases who received 100 to 200 mg. of cortisone acetate daily.

The effects of ACTH on circulating eosinophils are more pronounced, per milligram, than those of either cortisone or compound F, provided the subject has intact, responsive adrenal cortices. Thorn and associates¹⁰³ described a test for adrenal cortical insufficiency based on eosinopenic response to ACTH. In persons with Addison's disease there was little or no decrease in circulating eosinophils in four hours in response to a single 25 mg. dose of ACTH, whereas in subjects known to have normal adrenal cortices there was a 50 per cent or greater decrease. Roche, Thorn and Hills¹⁰⁴ suggested that this test might provide a good means for estimating prognosis in surgical patients with questionable adrenal cortical function, as well as for assaying adrenal cortical reserve in the postoperative period. The eosinopenic response also has been widely used as a means of estimating the adequacy of therapeutic doses of ACTH. However, eosinopenic response does not necessarily parallel clinical response, and eosinophil counts are obviously of little value in conditions characterized by eosinopenia.

Neoplastic Lymphoid Tissue. Exogenous cortisone or ACTH causes destruction of neoplastic as well as normal lymphoid tissue. In 1944 Heilman and Kendall¹⁰⁵ observed that a metastasizing transplantable tumor of mice did not grow when it was transplanted to mice receiving cortisone. Furthermore, there was a rapid regression of well developed tumors. Subsequent studies suggested that the tumor was a lymphosarcoma. The tumors usually recurred after withdrawal of treatment and then were refractory to the effects of the hormone.

In 1943 Murphy and Sturm¹⁰⁶ observed that removal of the adrenal glands greatly increased the susceptibility of rats to transplanted lymphatic leukemic tissue. In 1944 they¹⁰⁷ reported that administration of ACTH increased the survival of intact rats with transplanted leukemia. In a subsequent study, they¹⁰⁸ found that

rats from which the adrenals were removed and re-implanted intraperitoneally together with two additional adrenals from another rat showed an increased resistance to transplanted leukemia over that of control animals. Stoerk¹⁰⁹ observed that the growth of implanted lymphosarcoma in rats was retarded by daily administration of 2 mg. of cortisone or methyl testosterone. The greatest suppression of growth of the tumor was produced by injection of either cortisone acetate or methyl testosterone into pyridoxine-deficient animals.

In all of six patients with lymphomatous tumors, Pearson and associates¹⁸ observed dramatic decrease in the size of the lymph nodes and spleen during administration of ACTH or cortisone. Involution was first apparent after three days of treatment with ACTH and after six days of treatment with cortisone. In general, the tumors tended to increase in size when the hormones were withdrawn. The leukocyte counts on the blood of the four patients in the group who had lymphatic leukemia increased markedly during treatment. When the hormones were withdrawn, counts dropped below the initial levels. There was no definite change in the histologic picture of the lymph nodes. No complete clinical remissions occurred.

In a subsequent report Pearson, Eliel and Talbot¹¹⁰ described remissions in all of five previously untreated patients with acute leukemia to whom ACTH was administered. One of these had acute lymphatic leukemia and the other four had acute granulocytic leukemia. However, it was the opinion of the investigators that remissions of acute leukemia under the influence of ACTH are both incomplete and temporary. Subsequent reports have been in agreement with this opinion.¹¹¹

The findings of Pearson and associates have been confirmed by numerous observers in a variety of types of leukemia and lymphoid tumors. Most reports of the effects of ACTH in acute monocytic leukemia have indicated that no significant benefit occurs. Kinsell,¹¹² however, reported one case of acute monocytic leukemia in which partial remission possibly resulted from administration of ACTH. Eliel, Pearson and White⁶⁸ observed that ACTH, cortisone and compound F acetate were all capable of inducing some degree of regression of lymphoid tumors in a male patient who had chronic lymphatic leukemia.

The therapeutic results of administration of

ACTH and cortisone in neoplastic diseases of lymphoid tissue can be summarized by saying that many such diseases respond favorably, but the disease process recurs when treatment is withdrawn and response to further treatment is likely to be less satisfactory or may be entirely lacking. As a rule rather large doses of the hormones are necessary to produce benefit, with the result that other undesirable physiologic reactions are commonly observed.

The studies of Eliel, Pearson and associates^{18,21,68,113} have contributed valuable information concerning the metabolic effects of cortisone and ACTH on patients with lymphoid tumors. Among other features they have observed relatively tremendous losses of phosphorus in comparison to losses of nitrogen during administration of the hormones, the ratio of loss of phosphorus to nitrogen being such as to indicate destruction of lymphoid tissue which is high in phosphorus.

EFFECTS ON STATES OF ALLERGY AND HYPERSENSITIVITY

The laboratory studies of Rich and Gregory¹¹⁴ suggested a relationship between the hypersensitive state and the rheumatic diseases. Furthermore, a relationship between adrenal cortical function and hypersensitivity has long been suspected. Consequently, the demonstration of the dramatic effect of cortisone and ACTH on rheumatic diseases immediately suggested the possibility that these hormonal agents might favorably modify the hypersensitive state. This has proved to be the case. In addition, cortisone and ACTH are proving to be useful tools for study of the mechanism of the hypersensitive state.

Circulating Antibodies. In 1944 Dougherty, White and Chase¹¹⁵ presented evidence that administration of ACTH to immunized rabbits resulted in liberation of antibodies, presumably from lymphoid tissue. However, subsequent work has failed for the most part to support the view that adrenal hormones play a significant role in antibody liberation. For example, Fischel, LeMay and Kabat¹¹⁶ could not demonstrate an anamnestic rise in circulating antibody following administration of ACTH or roentgen therapy to rabbits, which had been immunized with crystalline ovalbumin, despite the occurrence of a concomitant decrease in the number of circulating lymphocytes. Similar negative observations have been reported by De Vries¹¹⁷

in rabbits immunized with egg albumin, and by Katzin and Goldman⁴² in rabbits immunized with goose erythrocytes. Stoerk and Solotovsky⁹⁶ observed a small, temporary increase in circulating antibodies in response to adrenal cortical extract in previously immunized rabbits. On the other hand, the same investigators found that a single 10 mg. dose of cortisone was followed by a decrease in circulating antibodies in all instances.

In contrast to the foregoing observations, Germuth and Ottinger¹¹⁸ presented evidence suggesting that cortisone and ACTH inhibit the development of the Arthus phenomenon in rabbits sensitized to egg albumin. There was an average of 100 per cent suppression of antibody by cortisone and 50 per cent by ACTH.

Studies of the influence of cortisone and ACTH on circulating antibodies of various kinds in patients with a variety of diseases have yielded essentially negative results.¹¹⁹⁻¹²¹

Anaphylaxis. Much of the evidence concerning the effects of cortisone and ACTH on the phenomenon of anaphylaxis seems to indicate that this process is not inhibited by these agents. For example, Harris and Harris¹²² and Dworetzky, Code and Higgins¹²³ found that cortisone did not prevent anaphylactic shock in guinea pigs sensitized with horse serum or solution of egg white, nor were Leger, Leith, and Rose¹²⁴ and the Friedlaenders¹²⁵ able to alter the occurrence of these reactions by administration of ACTH. Fischel¹²⁶ found that anaphylaxis, the Arthus reaction and other manifestations of union of antigen and antibody were not appreciably altered by administration of ACTH. On the other hand, Selye¹²⁷ reported that both cortisone and purified ACTH inhibited the anaphylactoid reaction of the rat to the intraperitoneal administration of egg white.

Skin Sensitivity. Reference has already been made to the conflicting reports of Fischel¹²⁶ and Germuth and Ottinger¹¹⁸ on inhibition of the Arthus reaction in rabbits by cortisone or ACTH.

Rose and associates¹²⁸ observed that reactions of skin tests to food or inhalant allergens, which were positive in three patients with asthma, were not altered by administration of ACTH. Bordley and associates¹²⁹ observed that skin reactions to inhalant allergens diminished in one patient with asthma but not in another as a result of administration of ACTH. Zeller, Randolph and Rollins¹³⁰ found that cutaneous reactions in two patients who were sensitive to

ragweed were not altered by treatment with ACTH in doses adequate to produce relief of allergic symptoms. Neither was there modification of the reactions at the sites of passive transfer as determined by gross and histologic studies. Administration of ACTH, however, markedly reduced the profuse tissue eosinophilia found in patients with untreated hay fever.

Studies of Histamine. Rose and associates¹²⁸ noted marked decreases or complete disappearance of urinary histamine in five of six patients with asthma during treatment with ACTH. In one patient urinary histamine was increased. All six patients showed a marked increase of urinary histidine. In a subsequent report Rose and associates¹³¹ noted a moderate to marked increase in urinary histamine following administration of ACTH to most patients with asthma with a return to normal as the clinical symptoms subsided. In four of five cases of rheumatoid arthritis there was little or no change in the excretion of histamine. Carryer and Code¹³² found that the *in vitro* addition of cortisone to the blood of rabbits previously sensitized to sheep erythrocytes had no effect on the release of histamine into the plasma which accompanied the hemolytic reaction produced by mixing the blood with sheep red cells. Furthermore the *in vitro* addition of cortisone did not have any effect on the histamine content of whole blood, on the distribution of histamine in the blood nor on the disappearance of histamine from blood during incubation.

Available evidence indicates that ACTH does not influence the development of bronchospasm in response to histamine in guinea pigs or asthmatic patients.^{125,133}

The foregoing studies suggest that ACTH and cortisone are not antihistaminic agents. The experiments of Rose and associates^{128,124} suggest that ACTH may alter the urinary excretion of histamine, but since the relation of the excretion of histamine in the urine to the development and maintenance of the hypersensitive state is not known, it is difficult to assess the importance of this effect on the allergic response.

Visceral Lesions in Hypersensitive States. In rabbits sensitized with horse serum, Berthrong, Rich and Griffith¹³⁴ found well marked vascular or cardiac lesions of periarteritis nodosa in eighteen of twenty untreated control animals and in only five of twenty animals treated with ACTH. Hackel, Portfolio and Kinney¹³⁵ observed that ACTH or cortisone did not protect

rats against the development of nephritis following administration of rabbit anti-rat kidney serum.

Clinical Observations. Numerous reports of favorable modification of the course of a variety of diseases of allergy and hypersensitivity by cortisone and ACTH have now appeared. Among these are exfoliative dermatitis due to iodine,¹²⁹ penicillin sensitivity,¹²⁹ generalized atopic dermatitis,¹³⁶ allergic dermatitis,¹³⁷ asthma^{128,129,138,139,140} and nasal allergy and polyps.^{128,129,139,140}

Thus the allergic process seems to be blocked at some point by cortisone and ACTH, but the site of blocking has not been identified. On the whole, the experimental evidence suggests that the various components of the allergic mechanism which have been closely scrutinized are not influenced by these agents. It appears, therefore, that the site of action is at a tissue level. In this connection, the influence of adrenal cortical steroids on permeability of membranes merits further consideration. There is some likelihood that the basic mechanism of action of the hormones in states of hypersensitivity may be closely related to their mechanism of action on the inflammatory diseases of connective tissue such as rheumatoid arthritis.

INFECTIONS, BACTERIAL ALLERGIC REACTIONS AND OTHER INFLAMMATORY REACTIONS

The profound effects of cortisone and ACTH on tissue reactivity are further illustrated by their capacity to modify local and systemic response to infections, bacterial products and miscellaneous inflammatory processes.

Tuberculosis. Hart and Rees¹⁴¹ found that prior administration of cortisone to mice resulted in a pronounced exacerbation of infection with *Mycobacterium tuberculosis* and a high mortality. Likewise, Spain and Molomut¹⁴² found that administration of 5 mg. of cortisone daily to guinea pigs sixteen days after infection with *Mycobacterium tuberculosis* resulted in lesions which were more extensive, more widely distributed and less localized than in the control animals which did not receive cortisone. Animals which were treated with streptomycin hydrochloride base in addition to cortisone showed considerably less involvement. After all therapy was stopped, however, nodular lesions appeared which were larger and more extensive than in a group of animals which had been treated with streptomycin in the absence of cortisone.

Freeman and associates¹⁴³ observed in two patients that the systemic symptoms of disseminated infiltrative pulmonary tuberculosis were ameliorated by administration of ACTH. Fever practically disappeared, coughing was diminished, and there was an increase in appetite and sense of well being. However, the sputum remained positive for *Mycobacterium tuberculosis* and in one case there was a definite spread of the pulmonary lesions during the period of administration of ACTH. Tompsett and associates¹⁴⁴ also found that administration of ACTH virtually abolished the systemic manifestations of advanced tuberculosis in four patients. Following withdrawal of ACTH the signs of acute illness returned abruptly. In patients with tuberculosis of the larynx, laryngeal ulceration and edema diminished and did not return after withdrawal of ACTH.

Hench and associates⁶² administered cortisone to two patients with tuberculous monoarthritis of a knee. In each case stiffness, tenderness and soreness on motion of the knee disappeared, but synovial biopsies and cultures showed that tuberculosis was still present.

Other Infections. Kass, Ingbar and Finland¹⁴⁵ reported that administration of ACTH to three patients with pneumococcal pneumonia and two with viral pneumonia was followed by prompt remission of clinical symptoms of acute illness. However, even after the patients with pneumococcal pneumonia became afebrile and asymptomatic, pneumococci were still present in the sputum. No evidence of an effect on the production of specific antibodies was found. Gil, Robles and Perrín¹⁴⁶ observed that the myocarditis induced in puppies by inoculation with *Schizotrypanum* (Chagas' disease) was improved from the point of view of clinical, electrocardiographic and radiologic changes by administration of ACTH. Nevertheless, foci of the organisms were still found in the myocardium of the treated dogs.

Reaction to Bacterial Products. Soffer and co-workers¹⁴⁷ observed that administration of 12.5 mg. of ACTH to rabbits before the provocative injection of meningococcus toxin completely inhibited the development of the Schwartzman phenomenon. This reaction is characterized by a severe confluent hemorrhagic necrosis at the site of an initial intradermal injection of meningococcus toxin following intravenous administration of a provocative dose. Likewise, Thomas and Mogabgab¹⁴⁸ observed that administration

of 10 mg. of ACTH to rabbits six and four hours before injection of the provocative dose of meningococcus toxin protected rabbits against the Schwartzman phenomenon in part.

Mirick¹⁴⁹ found that antibody was produced as promptly and in as high a titer in response to vaccination with pneumococcal polysaccharides in patients who were treated with ACTH or cortisone as in patients who were not so treated. Long and Favour¹⁵⁰ observed that administration of cortisone or ACTH obliterated the cutaneous reaction to beta hemolytic streptococci in nineteen of thirty-four patients. Those patients in whom the reaction was not obliterated showed a significant decrease of the induration and erythema.

Several investigators^{57,62,144,150,151} have noted that cutaneous hypersensitivity to tuberculin may be lost in some cases, but not in others, during administration of cortisone or ACTH. Woods¹⁵² observed that the focal reaction induced by subcutaneous injection of tuberculin in guinea pigs was blocked by ACTH.

Kass and Finland¹⁵³ found that the duration and intensity of the febrile response to an injection of killed typhoid bacilli in human subjects and in rabbits was reduced by previous administration of ACTH.

Chemically Induced Inflammation. Woods¹⁵² observed that cortisone given either topically or systemically to rabbits blocked the inflammatory reaction in the eyes due to such agents as glycerine or infusion of jequirity. Gross¹⁵⁴ found that cortisone in large doses had a strong inhibitory effect on chronic inflammations due to repeated injections of formaldehyde in rats and also on the acute inflammatory reaction induced by a single large dose of formaldehyde.

Pertinent Clinical Observations. The effects of cortisone and ACTH on bacterial and inflammatory processes may be of considerable clinical importance in patients who have intercurrent infections while under treatment with these agents. For example, Beck and associates¹⁵⁵ noted no fever or abdominal rigidity in two cases in which acute peritonitis developed during treatment with ACTH. The authors pointed out that some of the important signs and symptoms of acute perforation of an abdominal viscus with the development of peritonitis may be obscured by ACTH, thus making diagnosis difficult. Perera and associates¹¹ observed that the healing of a superficial pyogenic abscess was delayed during administration of cortisone to a patient

with hypertensive vascular disease. Plotz, Blunt and Ragan⁸⁸ reported a case in which moderately severe parotitis developed during administration of ACTH for disseminated lupus erythematosus. After the abscess was drained, it was noted that no granulation tissue formed for twenty days while ACTH was given, but following withdrawal of ACTH the wound healed. Thorn and associates¹⁵⁶ described a case of pemphigus which was arrested during treatment with cortisone and ACTH for twenty days but the patient died of staphylococcic septicemia while the hormones were still being administered.

Comment. One can speculate that the effects of cortisone and ACTH on the course of infections and inflammatory processes are analogous to the effects of these agents on such diseases as rheumatoid arthritis. It appears that in both instances the reactivity of the tissues to an injurious agent is inhibited. In the case of infections, the injurious agent is bacterial, whereas in the case of such diseases as rheumatoid arthritis, the nature of the injurious agent, if one actually exists, is unknown.

EFFECTS ON THE ENDOCRINE GLANDS

Since the functions of the several endocrine glands are interrelated to greater or lesser degree, it might be anticipated that the introduction of excess amounts of a secretory product of one gland might influence the structure or function of other glands. A limited amount of significant information, as well as some speculation, is now at hand concerning the effects of exogenous cortisone and ACTH on the endocrine glands; a part of this material will be reviewed here.

Anterior Pituitary

Adrenocorticotrophic Function. Depression of this function of the anterior pituitary by cortisone has been well demonstrated, and will be discussed in connection with the effects of cortisone on the adrenal cortex. Since exogenous hormones usually depress the corresponding function of the gland in which they normally originate, it is likely that ACTH as well as cortisone may depress adrenocorticotrophic function; however, evidence in support of this presumption is less clear than in the case of cortisone.

Other Functions. While there is some evidence that exogenous cortisone and ACTH influence the function of the thyroid and gonads, the reviewer is not aware of convincing evidence

that these effects, if they actually exist, depend on alteration of the corresponding trophic function of the anterior pituitary.

Structure. Golden, Bondy and Sheldon¹⁵⁷ found an increase in the total number of basophils, Crooke's hyaline cytoplasmic changes in these cells, and basophilic stippling of many of the chromophobe cells in the anterior pituitary of two patients who had received ACTH. They suggested that the observed changes might reflect storage of endogenous ACTH following stimulation of the adrenal cortices by exogenous ACTH. In addition, they described a focal increase of basophils resembling an adenoma in the anterior pituitary of a patient with myasthenia gravis who had received 975 mg. and 500 mg. of ACTH nine and six months, respectively, before death. Laqueur¹⁵⁸ described similar changes in five of eight patients after treatment with cortisone or ACTH. As early as five and a half days after the beginning of treatment there was replacement of basophilic granules by lumpy masses of hyaline basophilic material, resembling the changes described by Crooke in cases of Cushing's syndrome. These observations lend support to Kepler's¹⁵⁹ speculation that Crooke's hyaline changes and basophilic adenomas in the anterior pituitaries of patients with spontaneous Cushing's syndrome might be retrogressive changes secondary to an excess of adrenal hormones rather than changes primary in the causation of the syndrome.

Adrenal Cortex

Cortisone. That an excess of exogenous adrenal cortical hormones may induce atrophy of the adrenal cortices of animals was demonstrated in 1937 by Ingle and Kendall¹⁶⁰ in rats. In 1938 Ingle and Mason¹⁶¹ demonstrated atrophy of the adrenal cortices of rats into which pellets of cortisone had been implanted. Since then these and other investigators have described in further detail the atrophy induced by cortisone, and the recovery of normal adrenal structure and function following withdrawal of the hormone. Evidence has been obtained, first by Ingle,¹⁶² that the atrophy induced by cortisone is a consequence of depression of the adrenotrophic function of the anterior pituitary. Similar evidence has been obtained by Sprague and associates⁷⁶ in a study of a patient with panhypopituitarism. Sayers and Sayers¹⁶³ found that the administration of a variety of hormones of the adrenal cortex prior to subjecting rats to

stress inhibited the release of ACTH. Of the compounds tested, cortisone and compound F were the most potent in this regard.

In young adult male rats Winter, Silber and Stoerk²⁶ observed that adrenal cortical atrophy induced by large doses of cortisone involved the zona fasciculata and zona reticularis, while the zona glomerulosa was practically unaltered. Stebbins¹⁶⁴ likewise observed in rats that the two inner zones were more affected than the outer zone and that the lipoid and ketosteroid material of these two zones was depleted. Following withdrawal of cortisone acetate the cortex eventually resumed a normal appearance.

It will be recalled that Deane and Greep¹⁶⁵ found that the zona glomerulosa does not undergo atrophy in the hypophysectomized rat, while there is pronounced atrophy of the inner zones. This observation lends additional support to the concept that exogenous cortisone induces atrophy of the inner zones by depressing the adrenocorticotrophic function of the anterior pituitary.

Studies of patients by Forsham and associates¹⁶⁶ and by Sprague and associates⁷⁶ following prolonged treatment with cortisone have revealed four lines of evidence suggestive of depression of adrenal cortical function: (1) Some patients, following withdrawal of cortisone, complain of weakness and fatigability which may persist for variable periods.⁷⁶ (2) In certain patients the urinary excretion of 17-ketosteroids diminishes soon after administration of cortisone is begun and decreased excretion may persist throughout the period of administration of the hormone and for a time thereafter.^{76,166} (3) Response to a single 25 mg. dose of ACTH, as measured by per cent of decrease in the circulating eosinophils, is diminished.*^{76,166} (4) Response to 40 mg. of ACTH daily, as measured by increase in urinary 17-ketosteroids, is diminished.¹⁶⁶ (5) Adrenal cortical atrophy, involving the inner zones but sparing the glomerulosa, has been demonstrated at necropsy in some cases.⁷⁶ In addition, Holbrook¹⁶⁷ has noted that patients with rheumatoid arthritis may show a poor clinical response to ACTH for a time after withdrawal of cortisone.

Clinical Implications Concerning Cortisone. Is the apparent atrophy and depression of function induced by cortisone of any practical importance in the therapeutic use of the hormone? Experi-

ence to date is not adequate to provide a definitive answer to this question. There is no reason to suspect that the changes induced in the adrenals by cortisone are not reversible after administration of the hormone is stopped. It is possible that adrenal cortical function in a patient who had recently received cortisone might be inadequate under conditions of stress, such as trauma, fever or surgical operation. Perhaps this potential hazard would be greater soon after withdrawal of cortisone given by mouth than it would be soon after withdrawal of cortisone given intramuscularly, since the oral preparation is more rapidly dissipated from the body when administration is stopped. On the other hand, recovery of normal function may be more rapid after stopping the oral administration of cortisone. More experience with the clinical use of the hormone can be expected to provide answers to these questions.

Depression of adrenal cortical function has been turned to good use by Wilkins and associates¹⁶⁸ in the study of children with the adrenogenital syndrome due to congenital hyperplasia of the adrenal cortex. In these cases elevated values of urinary 17-ketosteroids and biologically active androgens were reduced by cortisone and there was suggestive evidence of depression of virilization.

ACTH. Administration of ACTH stimulates all known functions of the adrenal cortex. Morphologically this stimulation is expressed as hypertrophy and hyperplasia of the cortical tissue. These changes have long been known to follow administration of ACTH to animals, and have been described in a number of patients at necropsy.^{88,155,169} Evidences of stimulation regress rapidly when administration of the hormone is stopped.

Thyroid Gland

Although certain recent investigations suggest that exogenous cortisone and ACTH may depress thyroid function in animals and man, the entire subject needs more meticulous study than it has had to date. Most recent studies, particularly those on patients, do not provide adequate data to permit conclusions.

Winter, Silber and Stoerk²⁶ administered 3 mg. of cortisone acetate daily to normal rats. The average weight of the thyroid glands was slightly greater than that of untreated controls, but histologically the glands of the treated animals appeared normal. Money and associ-

* It was recognized that an effect of exogenous cortisone on the eosinophils themselves might have altered the response to ACTH.⁷⁶

ates¹⁷⁰ observed that both ACTH and cortisone decreased uptake of radioactive iodine by the thyroid of normal rats. Gabrilove and Soffer¹⁷¹ noted that administration of cortisone to adrenalectomized rats restored the response of the thyroid gland to epinephrine to normal as measured by uptake of radioactive iodine.

In patients the effect of cortisone and ACTH on thyroid function and the action of thyroid hormone has been studied by several different methods. For the most part, the resulting data are inconclusive. Reference has already been made to the rise in plasma cholesterol which may occur during prolonged administration of cortisone or ACTH. The possible relation of increase in plasma cholesterol to alteration in thyroid function has not been established with certainty. Perhaps more significant of depression of thyroid function is the observation of Hardy, Riegel and Erisman¹⁷² of a decrease in serum protein-bound iodine in all of nine patients with collagen diseases in whom determinations were made before and after treatment with cortisone (two patients) or ACTH (seven patients). The observed changes were probably too pronounced to be accounted for by dilution consequent to retention of water. No data on basal metabolic rates or other measures of thyroid function were given. Wolfson and associates⁴⁶ presented evidence of depression of thyroid function in seven patients with chronic rheumatic disease who received ACTH or cortisone continuously for prolonged periods. Hill and associates¹⁷³ reported that cortisone induced a rise in basal metabolic rate without changing the concentration of serum protein-bound iodine in one patient with postoperative hypothyroidism who was receiving suboptimal doses of desiccated thyroid. This evidence was interpreted as meaning that cortisone augmented the peripheral effect of a constant quantity of thyroid hormone.

In patients with Addison's disease Perera and associates¹¹ and Thorn and associates⁴¹ have reported a significant depression of thyroid activity during treatment with cortisone as measured by the rate of uptake of radioactive iodine. However, alterations in uptake of iodine by the thyroid gland are not necessarily paralleled by changes in its calorogenic function.

It is apparent that there is a need for critical investigation of the effects of cortisone and ACTH on isolated aspects of thyroid function that can be assessed in definitive fashion.

Clinical Implications. As yet, there is no satisfactory evidence that cortisone and ACTH are useful in the treatment of either exophthalmic goiter or adenomatous goiter with hyperthyroidism. Furthermore, Salassa¹⁷⁴ reported that cortisone acetate (100 mg. a day for seven days) or ACTH (1.4 gm. in seventeen days) failed to alter the exophthalmos or thyroid function of three patients with exophthalmic goiter without definite evidence of hyperthyroidism. Thorn and associates,¹⁵⁶ from their experience with ACTH and cortisone in the treatment of thyrotoxicosis, concluded that these hormones did not appear to offer any advantage over present methods of therapy. They noted slight improvement in four patients with malignant exophthalmos during administration of 40 to 80 mg. of ACTH daily for fourteen to nineteen days, but there was no measurable effect on the protrusion of the eyes.

In view of the fact that certain diseases which initially respond well to cortisone or ACTH lose their responsiveness when administration of the hormones is long continued, Wolfson and associates⁴⁶ and others have speculated that the loss of responsiveness might be related to depression of thyroid function. Evidence on this point at the time of this writing is not conclusive. For example, Knowlton and associates⁶⁰ observed that the metabolic response of a patient with primary myxedema to ACTH was essentially the same prior to and after institution of thyroid therapy. On the other hand, Hill and associates¹⁷³ reported that patients with untreated myxedema show a delayed and inadequate adrenal response to ACTH as measured by changes in the number of circulating eosinophils and in the excretion of 17-ketosteroids. Administration of desiccated thyroid restored a rapid response of the adrenals to ACTH as measured by these criteria. Certainly the possible relationship between endogenous thyroid function and responsiveness to cortisone and ACTH must have further critical study before conclusions can be reached.

Gonads

The occasional occurrence of amenorrhea in women and decreased libido in men during prolonged administration of cortisone or ACTH, and the common occurrence of these symptoms in spontaneous Cushing's syndrome suggest that these agents might exert some effect on gonadal function. Ingle,²³ in unpublished studies

made several years ago, found that administration of large doses of cortisone (5 to 10 mg. daily) to adult male rats caused some regression of the testes. In more recent studies, however, he has found that administration of 5 mg. of cortisone daily fails to induce loss of weight of either the testes or the seminal vesicles of the adult male rat. Winter, Silber and Stoerk²⁶ observed, likewise, that 3 mg. of cortisone daily for as long as six weeks produced no significant changes in the reproductive organs of male rats. On the other hand, Antopol⁵⁰ reported that the testes, seminal vesicles and prostate in mature mice which were treated with 2.5 mg. of cortisone for periods up to nineteen days were smaller than in untreated animals. It is possible that the changes observed by Ingle in his earlier studies and by Antopol were a reflection of the catabolic effects of cortisone rather than of a specific effect on the reproductive tract. To date little information is available concerning effects of cortisone and ACTH on gonadal structure and function in man.

EFFECTS ON CARDIOVASCULAR SYSTEM

For the most part, reports of cardiovascular effects of cortisone and ACTH have been limited to descriptions of the development of hypertension in an occasional case. There have been relatively few investigations of the effects of these agents on the cardiovascular system of animals. Ingle²³ pointed out the need for intensive study in this field, as there is little information concerning the relationship of adrenal cortical function to cardiac output, cardiac efficiency, circulation time, blood flow, and so forth.

Arterial Pressure. Reviews of the evidence concerning a relationship of the adrenal cortex to arterial hypertension and of ACTH and desoxycorticosterone acetate to hypertension have been published by Perera¹⁷⁵ and by Loofbourow and Palmer,¹⁷⁶ respectively.

Elevation of blood pressure and renal damage have been described by Selye¹⁷⁷ in unilaterally nephrectomized rats maintained on a high sodium, high protein diet during treatment with cortisone. In the rat cortisone did not interfere with the pressor effect of desoxycorticosterone acetate. Contrariwise, Friedman, Friedman and Nakashima¹⁷⁸ found that the increase in blood pressure which ordinarily followed the administration of desoxycorticosterone acetate to rats

did not occur in the presence of cortisone; nevertheless, increases in the weight of the heart and kidneys, due to desoxycorticosterone acetate, were not prevented by simultaneous administration of cortisone. Furthermore, cortisone caused lesions in the glomeruli of the kidneys which were additive to those caused by desoxycorticosterone acetate when both steroids were given together. Knowlton and associates¹⁷⁹ found that cortisone did not prevent the induction of nephritis in the rat by cytotoxic serum and that it had hypertensive effects in such rats. Guadino¹⁸⁰ observed that renal hypertension in the rat was not maintained after adrenalectomy but reappeared when cortisone was administered. The foregoing evidence indicates that cortisone may exert pressor effects in the rat under some circumstances, particularly in the presence of renal damage.

Although cortisone and ACTH have been reported to induce hypertension in certain patients with a variety of diseases, this has been the exception rather than the rule. The reviewer has the impression that hypertension has been reported more commonly in cases of disseminated lupus erythematosus than in other conditions, possibly because of the common presence of renal damage in the condition. Thus, Soffer, Levitt and Baehr¹⁸¹ observed hypertension in all of ten such patients and congestive heart failure in four during treatment with cortisone or ACTH. In some instances contamination of ACTH with pitressin may be a factor in the production of hypertension, but this is almost certainly not the sole factor.

Ransohoff and associates¹⁸² observed that administration of ACTH in conjunction with a low salt diet to a patient with uncomplicated essential hypertension did not alter the blood pressure, although the tetra-ethyl-ammonium chloride "floor" increased slightly. When ACTH was given in conjunction with a moderately high intake of sodium, the tetra-ethyl-ammonium chloride "floor" became further elevated and the blood pressure rose slightly. There is a need for additional systematic studies of the relation between intake of sodium chloride and the pressor effects of cortisone and ACTH.

In contrast to the pressor effect of cortisone and ACTH observed in some patients, Perera and associates¹¹ have reported slight depression of the resting blood pressure of hypertensive patients during administration of cortisone. One patient with Addison's disease, on the other

hand, had a rise in blood pressure during administration of cortisone.

Cardiac Function. In the course of the study by Ransohoff and associates¹⁸² already cited, a striking rise in stroke volume was noted when ACTH was administered in conjunction with a moderately high intake of salt. Precipitation of cardiac failure has been reported during treatment with cortisone or ACTH in several instances, usually in patients who had, or could be presumed to have, antecedent impairment of myocardial function. Somerville¹⁸³ reported improvement of abnormal electrocardiograms in patients with Addison's disease during treatment with cortisone.

Clinical Implications. The cardiovascular effects of cortisone and ACTH to which reference has been made should be borne in mind by the clinician who administers these agents to patients who have pre-existing hypertension, heart disease or renal disease.

Favorable, but frequently transient, modification by cortisone and ACTH of several diseases which affect the cardiovascular system, such as acute rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa and cranial arteritis, is now well documented.

EFFECTS ON GASTROINTESTINAL SYSTEM

Recent observations on the effects of cortisone and ACTH on the gastrointestinal system to be considered herein fall into three principal categories: effects on (1) gastrointestinal enzymes, (2) peptic ulceration and (3) inflammatory diseases of the gastrointestinal tract.

Gastrointestinal Enzymes. Spiro, Reifstein and Gray¹⁸⁴ observed in patients receiving ACTH an immediate and marked increase in the twenty-four hour excretion of uropepsin, a proteolytic enzyme originating in the stomach, probably from pepsinogen. This effect of ACTH was abolished by total gastric resection and was found to be absent in patients with gastric atrophy associated with pernicious anemia. Patients with adrenal insufficiency excreted no uropepsin in the urine and did not respond to ACTH. It would appear, therefore, that the effect of ACTH on excretion of uropepsin is mediated through the adrenal cortex and depends on the presence of functioning gastric glands. In addition, it was found that patients with active peptic ulcer frequently excreted increased amounts of uropepsin and that ACTH produced a further increase. Gray, Spiro and

Reifstein¹⁸⁵ found that administration of cortisone to patients with adrenal insufficiency resulted in an increased excretion of uropepsin.

Gray, Spiro and Reifstein¹⁸⁵ observed a direct correlation between the clinical activity of chronic ulcerative colitis and the titer of lysozyme in the stools. There was a decrease in the titer coinciding with clinical improvement resulting from administration of ACTH. Loeb¹⁸⁶ called attention to the observation of Meyer and Prudden that granulation tissue itself may be a good source of lysozyme, and that a decrease in the titer of this enzyme may be a reflection of decrease in granulation tissue rather than of modification of the underlying disease process.

Peptic Ulceration. In 1945 Ingle and associates¹⁸⁷ observed deep ulcers in the pyloric portion of the stomachs of two rats which were treated with large doses of compound F. In addition, one rat had several ulcers in the cecum with penetration of the wall at one point. Selye¹⁷⁷ has described gastrointestinal ulceration in rats subjected to various forms of stress, and it has been presumed that excessive secretion of adrenal cortical hormones under stress was a factor in the development of ulceration.

There is an increasing amount of circumstantial evidence that cortisone or ACTH, administered therapeutically to patients, may occasionally give rise to gastrointestinal ulceration. Beck and associates¹⁸⁵ described acute peritonitis in two patients who were receiving ACTH at the time of onset of gastrointestinal symptoms; the peritonitis of one of these patients was demonstrated at necropsy to be associated with a perforated duodenal ulcer. The duodenal ulcer appeared acute, there was no evidence of formation of fibrin in the ulcer, and there was no attempt by the omentum or other neighboring structures to wall off the lesion. The patient was not known to have had an ulcer previously. Habif, Hare and Glaser¹⁸⁸ described acute perforation of a duodenal ulcer nine hours after withdrawal of ACTH in a case of amyotrophic lateral sclerosis in which 80 mg. of the hormone had been given daily for twenty-nine days. There had been no previous gastrointestinal symptoms and at the time of the report the patient had been free of such symptoms for three months following dismissal from the hospital. Kuzell and Schaffarzick¹⁸⁹ described gastrointestinal bleeding in two patients with duodenal ulcer and in a third with prolapse of the gastric mucosa into the duodenum during

treatment with cortisone. Mason¹⁹⁰ observed a fatal gastrointestinal hemorrhage in the case of a patient receiving ACTH. At necropsy a duodenal ulcer with little inflammatory reaction in its base was found. The foregoing evidence and word-of-mouth descriptions of similar instances strongly suggest that gastrointestinal ulceration and hemorrhage may be complications of treatment with ACTH or cortisone although possible coincidence has not yet been ruled out with complete certainty.

Inflammatory Diseases of Gastrointestinal Tract. Marked symptomatic improvement in some cases of chronic ulcerative colitis during treatment with ACTH or cortisone has been reported by several observers.¹⁹¹⁻¹⁹³ Although some observers have reported subsidence of the gastrointestinal inflammation, as visualized proctoscopically, others have reported symptomatic improvement without evidence of healing. There is little to suggest that administration of cortisone or ACTH ever results in complete healing. Astwood and associates¹⁹⁴ observed unequivocal symptomatic improvement in four patients with regional enteritis during administration of ACTH. Several observers have noted clinical improvement in viral hepatitis during treatment with cortisone or ACTH, but the unpredictable course of this disease makes it difficult to evaluate the role of the treatment in the observed improvement. In any event, the favorable effects of cortisone and ACTH on inflammatory diseases of the gastrointestinal tract appear to be similar to their effects on inflammatory processes elsewhere and do not imply that pituitary or adrenal dysfunction plays an etiologic role in these conditions. Their use in the treatment of conditions which are known on occasion to cause gastrointestinal perforation may be attended by some hazard.

EFFECTS ON THE NERVOUS SYSTEM

The nervous system does not escape the physiologic activity of cortisone and ACTH. Observations of effects on the nervous system have been limited to those made during administration of the hormones for therapeutic purposes. Few physiologic studies on the nervous systems of animals have been reported.

Physiologic Studies. Selye¹⁹⁵ described the anesthetic effect of a number of steroid compounds. In his study, anesthetic activity was indicated by loss of the righting reflex in partially hepatectomized immature female rats

during intraperitoneal administration of the steroid. Among the numerous compounds tested, cortisone had relatively low activity.

Woodbury and Sayers¹⁹⁶ observed that administration of 2 mg. of cortisone daily to rats increased the excitability of the brain as indicated by a lowering of the threshold for induction of seizures by electroshock. Woodbury and associates¹⁹⁷ had previously noted that desoxycorticosterone acetate had the opposite effect. Both ACTH¹⁹⁷ and cortisone¹⁹⁶ were found to be effective in preventing elevation of the seizure threshold by desoxycorticosterone acetate.

Thorn and Forsham⁹⁸ noted that some patients with Addison's disease exhibited a progressive acceleration of the brain waves with a return of abnormal electroencephalographic tracings toward normal during treatment with cortisone. Hoefer and Glaser¹⁹⁸ reported changes in the electroencephalogram during treatment with ACTH in thirteen of fifteen patients with various diseases not characterized by adrenal cortical insufficiency. Abnormalities of the electroencephalogram which existed prior to treatment gradually became more pronounced. The abnormalities observed included slightly slow records in seven patients. The changes which occurred under the influence of ACTH could not be correlated with the dose of the hormone nor with alterations of the blood sugar or plasma electrolytes. Careful study of more patients with and without adrenal cortical insufficiency will be necessary to reconcile the observations of Thorn and Forsham with those of Hoefer and Glaser.

Clinical Observations. Several untoward neurologic and psychiatric manifestations have been observed during treatment with cortisone or ACTH. Convulsive seizures have been reported with sufficient frequency to suggest some relationship to cortisone^{69,181} or ACTH.^{66,181,194,199,200} Reference has been made to the observation of Woodbury and associates^{196,197} that cortisone is capable of increasing the excitability of the brain of rats as indicated by a lowering of the threshold of electroshock seizure. This may have some bearing on the occurrence of convulsive seizures in patients.

Stickney²⁰¹ observed the case of a child, five years old, afflicted with acute leukemia who lapsed into coma on completion of treatment with ACTH and eventually died. At necropsy degenerative changes were found in the cells of the cerebral cortex. Engel²⁰² observed an

boy with Still's disease who developed hypertension and who lapsed into coma during treatment with ACTH. He subsequently had convulsions and continued marked diffuse abnormalities in the electroencephalogram.

A wide variety of psychic reactions, presumably hormonally induced, have been observed in occasional patients during treatment with cortisone or ACTH.^{13,24,62,88,121,181,189,203-206} These include mild degrees of stimulation, sleeplessness, euphoria, manic behavior, depression and frank psychosis. Rome and Braceland²⁰⁴ made psychiatric observations on a series of twenty-six patients with various physical diseases during treatment with cortisone or ACTH. They emphasized the view that major psychic alterations under the influence of the hormones in most instances represent intensification of pre-existing disorders of personality.

Cortisone and ACTH, particularly the latter, have had therapeutic trial in a variety of neurologic²⁰⁷⁻²¹⁰ and psychiatric^{198,204,211,212} conditions. In general, the therapeutic results have not been impressive.

Regardless of therapeutic utility, it is apparent that cortisone and ACTH have profound effects on the neurologic and psychic functions of some individuals. It is probable that they will provide a useful tool for the study of mechanisms involved in various psychiatric states and will give merited emphasis to the biochemical approach to these problems.

COMMENT

In this review emphasis has been placed on certain effects of cortisone and ACTH which seem to be of actual or potential clinical importance. It is becoming increasingly evident that these hormones are capable of influencing many physiologic processes, with varied clinical consequences. Furthermore, it is probable that even more physiologic effects remain to be described. Certainly, most of the effects which have been described up to the time of this writing are poorly understood, and little progress has been made toward correlating measurable physiologic activity with therapeutic effects. Ingle²³ has epitomized the limitations of present day understanding of the activity of cortisone as follows: "The consequences of cortical hormone action spread through the organism in a manner reminiscent of the waves caused by the impact of a stone in a pool of water, but the

point of impact of the hormone remains unknown for the present."

Notwithstanding the lack of precise knowledge of the mode of action of cortisone and ACTH, it is important for the clinician to have a broad understanding of their effects in so far as they have been described. The safe and effective therapeutic use of these agents depends on such understanding. Even though administration of cortisone and ACTH to patients suffering from certain diseases brings about prompt improvement, and withdrawal is usually followed by prompt return of symptoms, yet there is no convincing evidence that the conditions which are thus favorably modified are actually associated with a deficiency of adrenal hormones. Strong evidence indicates that this is not so.*

As a corollary, it would appear that a state of hormonal excess of some degree must be established before a favorable clinical effect can be achieved. Associated with such a state is the possibility of diverse physiologic effects in addition to those which are therapeutically desirable. Fortunately, in many instances, favorable clinical effects can be realized before other less wanted types of activity manifest themselves, particularly if small doses or short periods of administration suffice for therapeutic benefit. Since this is not always the case, a full appreciation of the physiologic potentialities of the hormones is desirable.

The effects of cortisone and ACTH which seem to be most prominently involved in their therapeutic activity in several diseases are their capacity to inhibit the reactivity of mesenchymal tissues and block reactions of allergy and hypersensitivity. Possibly these effects are closely allied. They may manifest themselves clinically in the dramatic reversal of rheumatoid arthritis, states of hypersensitivity and a variety of other diseases. But they may also show themselves in inability to heal a wound, react to infection or wall off a perforating ulcer. Thus, an effect which may be therapeutically useful under some circumstances may be harmful under others.

The use of cortisone and ACTH as tools for the physiologic investigation of a variety of human diseases needs further exploitation. While they seem to be assured of a place in practical therapeutics, it is even more impor-

* Obvious exceptions to this statement are conditions of frank adrenal cortical insufficiency, such as occur in Addison's disease and panhypopituitarism or after adrenalectomy.

tant that they should contribute to an understanding of the mechanisms of certain categories of disease which are now unsolved medical mysteries.

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Advances in the Diagnosis and Treatment of Adrenal Insufficiency*

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RECENT developments in the field of adrenal hormone physiology and chemistry have made great refinements possible in the diagnosis and treatment of adrenal cortical insufficiency. Historically, the administration by Osler in 1896 of an oral glycerine extract prepared from hog adrenals marked a milestone on the road toward effective specific replacement therapy.¹ Subsequently, more potent preparations of adrenal cortical extracts were devised;^{2,3} these, in turn, were followed by the isolation and identification of corticosterone, dehydrocorticosterone, the 11,17-oxysteroids, Compounds E and F by Reichstein and Kendall, the partial synthesis of desoxycorticosterone and more recently the synthesis of Compounds A, B, E and F.⁴ So potent are the synthetic adrenal steroids now available in restoring endocrine balance that complete bilateral adrenalectomy may be carried out in man as an experimental therapeutic approach to the modification of such serious disorders as hypertensive cardiovascular disease.^{5,6} Thus the goal of substituting pure chemical compounds for the adrenal cortex has become a reality after a half century of intensive research.

Of importance equal to the discovery and synthesis of the several adrenal cortical steroids has been the isolation of pituitary adrenocorticotrophic hormone (ACTH)⁷⁻⁹ which has made possible, for the first time, the specific stimulation of the adrenal cortex, thus permitting a simple measure of adrenocortical reserve.¹⁰ Its

use has not only brought to light mild chronic adrenal cortical insufficiency but has made possible the detection, even the prediction, of temporary states of acute adrenal exhaustion.¹¹

It is the purpose of the present discussion to summarize our clinical experiences with these new tools for the diagnosis and treatment of adrenal cortical insufficiency.

DIAGNOSIS OF ADRENAL CORTICAL INSUFFICIENCY

Adrenal cortical insufficiency may occur as a result of disease of the adrenal gland itself (primary) or as a consequence of inadequate secretion of ACTH due to anterior pituitary or hypothalamic disease (secondary). Acute adrenal cortical insufficiency may develop with startling rapidity and often presents special diagnostic problems. Until recently the detection of adrenal insufficiency, either chronic or acute, was essentially a clinical problem and subject to many errors. While the picture of classical Addison's disease may be obvious enough, many atypical syndromes associated with asthenia or pigmentation arise which tax the judgment of even the shrewdest clinician. Fortunately, it is now possible to supplement bedside acumen with a group of reliable laboratory measurements which make possible more precise evaluation of adrenocortical function in the majority of cases. It is the purpose of the present discussion to summarize our own experience with these newer procedures as aids to

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clinical diagnosis. The clinical picture itself has been exhaustively discussed elsewhere.¹²⁻¹⁷

Laboratory Diagnosis

Changes in Adrenal Morphology as a Criterion of Adrenal Cortical Reserve. Adrenal cortical biopsies are impractical and even when obtained are unsatisfactory as a diagnostic aid in most types of adrenal cortical derangement since there is no agreement as to the function of the different portions of the adrenal cortex.^{18,19} However, in cases of adrenal insufficiency associated with either carcinoma or androgenic hyperplasia of the adrenal cortex²⁰ biopsies are of diagnostic value. Perirenal air insufflation will occasionally outline an abnormally large adrenal cortex by x-ray but the dangers associated with this procedure have prevented its general use.

A positive x-ray shadow at the level of the first lumbar vertebra raises the question of adrenal cortical calcification. Such calcification is most often due to old tuberculosis of the adrenal gland but may also occur following hemorrhage and fungus infections. Adrenal calcification does not in itself indicate adrenal cortical insufficiency. Of 123 patients with Addison's disease in whom a satisfactory abdominal x-ray was obtained during the past eight years,* fifteen patients (i.e., 12 per cent) showed adrenal calcification, bilateral in 10, unilateral in 5. On the other hand, four patients were seen during this period with adrenal calcification in whom a positive diagnosis of adrenal insufficiency could not be made. In two of these calcification was bilateral and in two, unilateral.

Changes in Urinary Steroid Excretion. The urinary excretion of so-called 11-oxysteroids is very low in both primary and secondary adrenal cortical insufficiency.²¹ The determination of urinary 17-ketosteroids, although a less specific index of adrenal cortical activity, is more easily carried out and quite satisfactory for clinical purposes. In the female the adrenal cortex is the only important source of such compounds or their precursors, whereas in the male the testes make an additional contribution; it is for this reason that 17-ketosteroid excretion is normally 50 per cent greater in the male (8-23, av. 15 mg. per twenty-four hours) than in the female (5-12, av. 10 mg. per twenty-four hours). In Addison's disease the daily excretion approaches zero in

the female (0.1-8.6, av. 3.0) and about 5.0 mg. in the male (1.0-8.0, av. 4.2).¹⁷ Values close to zero in a male patient suggest secondary rather than primary adrenocortical insufficiency.

Characteristic Changes in the Electroencephalogram. The electroencephalogram in Addison's disease is characterized by a decrease in the predominant frequency and the presence of short bursts of low frequency.²² In twenty-four patients with untreated Addison's disease the average predominant frequency was 8.2 waves/second (range 5 to 11), compared with a normal of 10 waves/second (range 8-12). The characteristically slow electroencephalogram, while reversed by cortisone,²³ is not improved by DCA sufficient for the maintenance of normal hydration. Since the same type of slowing occurs with hypothyroidism, this finding is a sign of persistent deficiency of 11,17-oxysteroids only if the former can be excluded.

Changes in the Electrolyte Balance. A serum sodium concentration below 136 mEq. per L., associated with a serum Na/K ratio below 30 (both being expressed as milliequivalents per liter), suggests adrenal cortical insufficiency.²⁴ It should be emphasized, however, that serious alteration in serum electrolytes may not be found in early or mild cases of Addison's disease. As a corollary to chronic sodium loss, dehydration and contraction of the circulating blood volume a small heart size is found invariably unless coexisting primary heart disease or thyrotoxicosis is also present.

Recently the salivary sodium:potassium ratio has been shown to vary inversely with the state of adrenal cortical activity.²⁵ While the mean ratio in normal individuals was found to be 1.3 ± 0.5 , that in patients with untreated Addison's disease ranged above 2.2 ± 0.5 . In the presence of a significantly lowered serum sodium, to 132 mEq. per L. or less, the salivary Na:K ratio may not show the elevation characteristic of adrenal insufficiency.

Other less practical tests are the demonstration of a low sodium concentration in sweat²⁶ and a tendency during metabolic balance studies to lose sodium and gain potassium.²⁷

Changes in Carbohydrate Metabolism. Although the lack of cortisone and Compound F leads to a fall in fasting blood sugar, the change is too small to be of specific diagnostic value.

The intravenous glucose tolerance test is often followed by a reactive hypoglycemia. Since such a procedure in patients not receiving cortisone

* X-ray studies were made in the Department of Roentgenology, Peter Bent Brigham Hospital, under the direction of Dr. Merrill C. Sosman.

is often followed by a severe febrile reaction up to twelve hours after the end of the infusion,²⁸ this test should not be employed in making the diagnosis of Addison's disease. A flat oral glucose tolerance curve,²⁹ frequently observed in Addison's disease, is of little diagnostic significance

potentiation of its destruction by the liver. It is also possible that adrenal steroids may have a direct diuretic effect on renal function, independent of their influence on antidiuretic hormone.³³ False positive "water tests" may occur in patients with liver or kidney disease.³² It

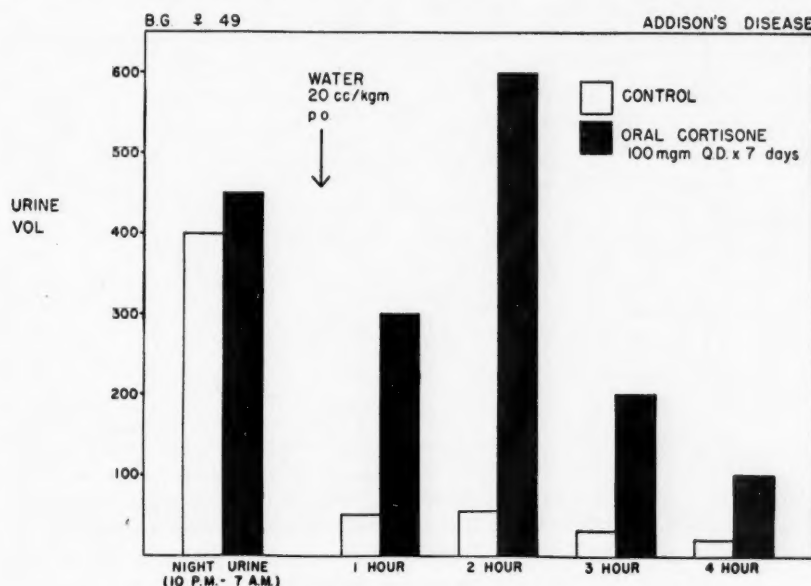


FIG. 1. Effect of oral cortisone acetate on the water test.

other than indicating impaired gastrointestinal absorption of glucose. It bears no relationship to changes in intermediary carbohydrate metabolism.

Hematologic Changes. Adrenal cortical insufficiency is usually accompanied by a low total white count, an increased percentage of lymphocytes³⁰ and a normal to high number of circulating eosinophils.³¹ In the presence of primary or secondary hypothyroidism with adrenal cortical insufficiency the eosinophil count may on occasion be lower than 100 (normal range: 150–350/cu. mm.). The characteristic anemia is often masked by hemoconcentration.

Tests for Adrenal Cortical Response to Stimulation. Adrenal cortical response may be elicited nonspecifically by testing the effect on the adrenal cortex of sudden changes in the metabolic state of the body in the so-called "tolerance tests."

The *Robinson-Kepler-Power water test*³² will demonstrate inability to show normal water diuresis. This is thought to depend upon the fact that adrenal 11,17-oxysteroids are required to decrease the amounts of pituitary antidiuretic factor, known to be elevated in Addison's disease, either through suppression of its secretion by the posterior lobe of the pituitary or possibly through

has been shown that pre-treatment with cortisone will lead to a return to normal water diuresis in a patient with Addison's disease²³ whereas desoxycorticosterone treatment will not, at least in the clinical dosage employed. An example using oral cortisone is shown in Figure 1.

In the *Wilder test*³⁴ the adrenal cortex is put under metabolic stress by the withdrawal of salt from the diet and the addition of potassium in order to induce additional sodium loss. If over the course of a two-day period an adrenal crisis develops or the urinary loss of sodium and chloride is progressive, the inadequacy of electrolyte regulation is clearly demonstrated, provided that primary renal disease has been excluded.

The use of a *twenty-four-hour fast* is the most satisfactory method of establishing the status of the carbohydrate-regulating function of the adrenal cortex. All meals are omitted after 5 P.M. and the patient's blood sugar measured at three-hour intervals after 8 A.M. the following morning. The absence of hypoglycemic symptoms at the end of a twenty-four- or thirty-six-hour fast excludes severe insufficiency of adrenal carbohydrate-regulating factors but gives no information as to the secretion of other adrenal cortical factors. When hypoglycemic symptoms

are produced, they are likely to appear at higher blood sugar levels than are usually found with other types of hypoglycemia. In cases of adrenal cortical insufficiency maintenance of blood sugar levels may be re-established by the administration of cortisone. (Fig. 2.)

eosinophils as an indicator of 11,17-oxysteroid titer in the blood are not controlled solely by these hormones but vary depending upon the rate of production (high in allergy and low in hypothyroidism or bone marrow invasion by neoplasm) and destruction in the reticuloendo-

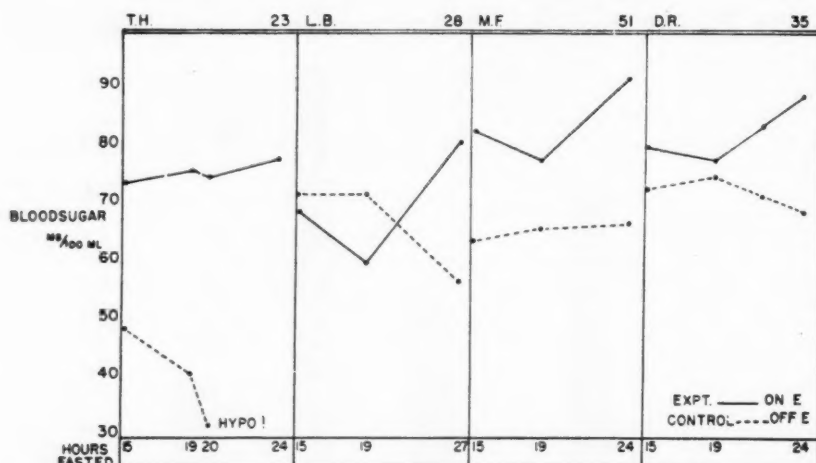


FIG. 2. Effect of Compound E on blood sugar levels during prolonged fast in four female patients with severe Addison's disease. This material was obtained in collaboration with Dr. Leslie L. Bennett.

The most specific stimulation of the adrenal cortex may be achieved by the administration of anterior pituitary adrenocorticotrophic hormone, or ACTH.³⁵ Use has also been made of the fact that epinephrine will induce the endogenous secretion of ACTH in the presence of a normal hypothalamic-pituitary relationship.³¹

The ACTH tests. By the administration of ACTH it is possible to determine the ability of the adrenal cortex to respond to its natural activator. The procedure has the virtues of simplicity and specificity. It tests the capacity of the gland to respond to a stimulus above that which is normally present in the resting state. It indicates, therefore, the reserve capacity of the gland.

Four-hour ACTH test: Direct stimulation of the cortex is achieved by the intramuscular administration of 25 mg. of ACTH and the number of circulating eosinophils is followed as the measure of adrenal response. The maximum change occurs at approximately four hours after stimulation and reflects the release of 11,17-oxysteroids from the activated cortex.³⁵ It was previously shown that 11-oxysteroids in comparable dosage fail to depress circulating eosinophils, and desoxycorticosterone likewise showed no effect at lower dosage levels.³⁶ The

thelial system. They therefore represent only a relative indicator of adrenal cortical activity.

A summary of the results obtained with the four-hour test in seventy-five subjects is shown in Figure 3. A fall of 50 per cent in circulating eosinophils four hours after stimulation is considered the lower limit of normal. The majority of normal subjects showed a drop of 70 per cent or more. In contrast, a group of fifty Addisonian patients exhibited an average decrease of only 7 per cent and approximately one-third responded with an eosinophil rise rather than a fall.

Patients with hypopituitarism are intermediate in response, with an average fall of 31 per cent, the magnitude of change depending upon the degree and duration of adrenal cortical involution.

It is apparent that some overlap may occur between the response of patients with primary adrenocortical insufficiency and those with panhypopituitarism. Rarely, on the other hand, a false positive result may occur in the presence of allergy if the production of eosinophils is sufficiently rapid to prevent a significant reduction in circulating eosinophils. In this case the question of adrenal response may be answered by the oral administration of 50 mg. of corti-

sone³⁷ or intravenous injection of 50 cc. of aqueous adrenal cortical extract³¹ and a subsequent eosinophil count after four hours. If an eosinophil decline of 50 per cent or more occurs, then the absence of response to ACTH implicates the adrenal cortex and not a refractory eosinophilia.

of 17-ketosteroids is chosen only because it is technically less complicated, just as the eosinophil count represents a still simpler, although even less specific indicator in the four-hour test.

In the normal individual the forty-eight-hour eosinophil fall averages 91 per cent and the ketosteroid excretion is significantly increased.³⁹

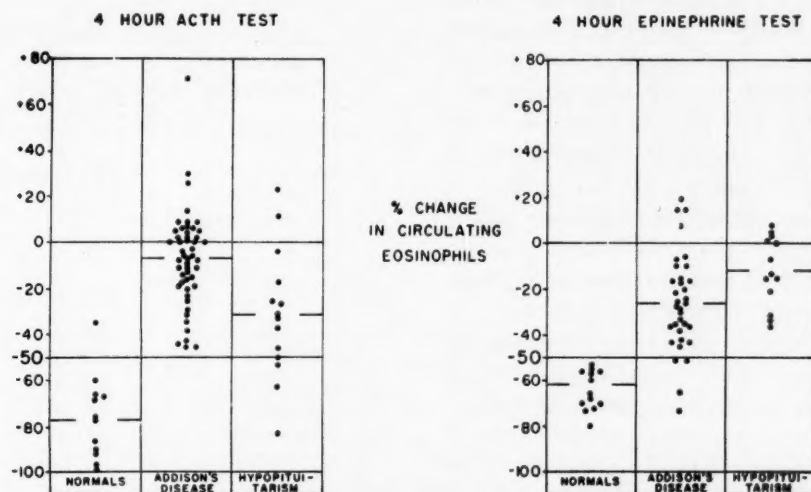


FIG. 3. A comparison of the four-hour ACTH and epinephrine tests. The broken horizontal bars denote the mean values for each group.

The determination of changes in the urinary *uric acid:creatinine ratio*, as suggested in the original test,¹⁰ is no longer practiced. The interpretation may prove unreliable unless the purine intake is standardized at a relatively high level.³⁸

Forty-eight-hour ACTH test: When the four-hour eosinophil test fails to provide a clear-cut demarcation between primary and secondary adrenocortical disease, recourse may be had to the forty-eight-hour test. Here the initial 25 mg. dose of ACTH is followed by 10 mg. every six hours for a total ACTH administration of forty-eight hours. The last eosinophil count is taken four hours after the last injection of 10 mg. of ACTH. A longer period of stimulation is thereby utilized, providing additional opportunity for the activation of a cortex which is only involuted and not destroyed. In addition to the forty-eight-hour eosinophil response the increase in urinary 17-ketosteroid excretion is followed as a corroborative measure of cortical stimulation.³⁵ Table I summarizes the results of this procedure in forty-five subjects. It should be pointed out that the urinary determination of formaldehydogenic steroids ("11-oxysteroids") would be an even more sensitive and specific indicator of changes in adrenal cortical activity which occur in the forty-eight-hour test; the determination

In the Addisonian, in contrast, the eosinophils consistently fail to fall 50 per cent and the increase in ketosteroid excretion is less than 3.0 gm. per twenty-four hours. In fact, one-half of the patients with Addison's disease will demonstrate either a rise in eosinophils or a fall

TABLE I
FORTY-EIGHT-HOUR ACTH TEST

	Eosinophil Change—%		Change in 17-Ketosteroid Excretion	
	Mean	Range	Mean mg./24 hr.	Range mg./24 hr.
Normal controls (13) . . .	-91	(-84 to -100)	9.9	(4.7 to 31.7)
Addison's disease (20) . .	0	(81 to -37)	0.3	(-2.9 to 2.6)
Hypopituitarism (12) . . .	-58	(0 to -95)	3.5	(1.4 to 10.0)

in 17-ketosteroid output, or both. The test provides an excellent delineation of adrenocortical insufficiency. A representative case follows:

J. C. (P.B.B.H. No. 6B713), a forty-one year old physician, entered the hospital with a two-year history of increasing weakness and fatigability, weight loss, gastrointestinal upsets, salt-craving and pigmentation. The four-hour ACTH test revealed a 5 per cent eosinophil fall; the

forty-eight-hour ACTH test showed a 48 per cent eosinophil rise and 1.1 mg. per twenty-four hour decrease in 17-ketosteroid excretion. The diagnosis was chronic adrenal insufficiency.

The response of the patient with pituitary insufficiency and secondary adrenocortical atrophy is quite variable. The eosinophil drop is usually greater than that of the Addisonian and in the majority of cases exceeds 50 per cent. The change in 17-ketosteroid excretion is less constant and in some cases the increase fails to attain a normal standard value. The greater response of the eosinophils in these patients is in keeping with the very marked sensitivity of this index of cortical stimulation. This is exemplified in the cases in which an essentially normal eosinopenia occurs with ACTH administration but without a significant rise in ketosteroid excretion, a combination compatible with active stimulation of an adrenal cortex still capable of responding to stimulation but largely inactive. The following case is cited:

P. C. (P.B.B.H. No. R4887), a twenty-three year old male, entered the hospital because of weakness and attacks of faintness, palpitation and sweating. Three years previously a malignant chromophobe adenoma of the pituitary had been removed, followed by several courses of irradiation. Body hair was diminished, the BMR was decreased and testicular atrophy was present. A forty-eight-hour ACTH test was performed which revealed the following: eosinophils, 75 per cent fall; 17-ketosteroids, increased 2.3 mg. per twenty-four hours; *impression*: Hypopituitarism with secondary adrenal cortical involution.

Other patients with pituitary insufficiency may show a much more active response to ACTH in terms of both eosinophils and ketosteroids, indicating only a moderate involution of the adrenal cortex. In this type of patient the differentiation from primary adrenal insufficiency is more clearcut.

S. K. (P.B.B.H. No. G9611), a twenty-nine year old male, entered the hospital following irradiation for a pituitary chromophobe adenoma. Examination disclosed muscular weakness, weight loss and hypotension; no pigmentation was noted. A forty-eight-hour ACTH test produced the following response: eosinophils, 59 per cent fall; 17-ketosteroids, increased to 10.0 mg. per twenty-four hours. The diagnosis was hypopituitarism, with a mildly atrophic adrenal cortex, capable of good stimulation.

Intravenous ACTH test: The basis of this test is the profound adrenocortical stimulation elicited in a relatively short time by the intravenous infusion of a minimal quantity of ACTH. This avoids the variable factors of absorption and local inactivation associated with the intramuscular route.

TABLE II
EOSINOPHIL RESPONSE TO THE INTRAVENOUS
ADMINISTRATION OF ACTH OVER AN EIGHT-
HOUR PERIOD IN SIX REPRESENTATIVE
PATIENTS

Pa- tient	Diagnosis	ACTH Dose (mg.)	Eosinophils/cu. mm.					Eosinophil Fall—%	
			0°	4°	8°	12°	24°	at 4 hr.	at 8- 12 hr.
J. P.	Addison's disease	20	179	104	179	188		42	0
M. C.	Bilateral adrenal- ectomy	20	774	768	753	738	742	1	4
W. C.	Bilateral adrenal- ectomy	20	170	159	181	185	175	6	0
E. S.	Rheumatoid arthritis	20	463	209	9	3	417	55	99
F. C.	Nephrosis	15	106	44	6	0	151	68	100
M. T.	Psoriasis	12	418	132	9	6	346	68	98

Twenty mg. of ACTH in 500 cc. saline or 5 per cent dextrose is infused over an eight-hour period. The typical results obtained in adrenal cortical insufficiency, as opposed to normal adrenal states, are shown in Table II. A considerable rise in 17-ketosteroid excretion (3.4 to 22.0 mg. per twenty-four hours) on the day of the infusion, in the absence of adrenocortical insufficiency, may be measured along with the changes in circulating eosinophils. Indeed, the magnitude of this rise affords a rapid, accurate and quantitative measure of the maximal adrenal cortical reserve available.⁴⁰

The Four-hour Epinephrine Test. The participation of epinephrine in the normal activation of the hypothalamic-pituitary-adrenocortical axis has been well established.³¹ It is apparent that in order for epinephrine to be effective the hypothalamic and anterior pituitary stores of hormone must be adequate and the capacity of the adrenal cortex to secrete steroid hormones must be intact. With this in mind the epinephrine test³¹ was devised as a supplement to, but not as a substitute for, the ACTH tests. Since variabilities in response to epinephrine are obtained in different states of adrenal cortical activity, it is important to re-emphasize the limitations of this test and to point out the specific situations in which it may be useful. Our

experience with this test in a group of normal subjects and a group of patients with pituitary and adrenal cortical insufficiency is reviewed in Figure 3.

In Addison's disease a fall of 50 per cent or more in circulating eosinophils is usually not

TABLE III
FOUR-HOUR EOSINOPHIL RESPONSE TO ACTH
AND EPINEPHRINE IN PATIENTS WITH
ADDISON'S DISEASE, BOTH BEFORE AND
AFTER INSTITUTION OF
CORTISONE THERAPY

Patient	Sex	ACTH Response —%		Epinephrine Response—%	
		Before	After	Before	After
D. C.	F	0	-20	0	-49
H. W.	M	-16	-69	+15	-72
J. P.	M	-8	-42	0	-48
S. B.	M	0	-33	-15	-32
E. M.	F	-28	0	-10	-64
V. A.	F	0	0	-48
M. H.	F	-12	0	-20

obtained. However, a normal response may occasionally be produced in spite of obvious evidences of Addison's disease. Of thirty-four patients with Addison's disease four showed a fall in eosinophils greater than 50 per cent, even though the same patients failed to respond normally to test doses of ACTH. It has been previously shown³¹ that by increasing the dose of epinephrine to 1.5 mg. and administering it intravenously over a one-hour period, falls in circulating eosinophils approaching and occasionally actually exceeding 50 per cent could be obtained. At present there is no proven explanation for this eosinophil response. Epinephrine, therefore, should never be used to test for adrenal cortical function when ACTH is available.

It has been interesting to observe in certain Addisonian patients following cortisone therapy for varying periods of time that with the improvement in the ACTH test there is also a return of response to epinephrine. (Table III.) This might mean that more adequate substitution therapy has permitted reaccumulation of increased levels of hormones within the adrenal cortex and the anterior pituitary, analogous to the increased insulin content of the pancreas in animals treated with exogenous insulin. In this

way, a relatively normal response of short duration might be possible following sudden stimulation. Thus a positive response to epinephrine (a fall in eosinophils) might not be taken as definite evidence of an intact adrenal cortex.

While it is apparent that the epinephrine test cannot, by itself, be used for the diagnosis of primary adrenal cortical insufficiency, the experimental³¹ and clinical evidence suggests that it may be a fairly reliable test for secondary adrenal cortical insufficiency due to panhypopituitarism.

Differential Diagnosis of Adrenal Insufficiency

None of the symptoms and signs of adrenocortical insufficiency is in itself distinctive and it is for this reason that this rather rare disease so often enters the differential diagnosis in general medicine. Thus Addison's disease must be separated from the fatigue and muscular weakness of neurasthenia, myasthenia gravis, thyrotoxicosis, hyperparathyroidism, chronic renal disease and chronic tuberculosis; from the weight loss, hypochlorhydria, gastrointestinal complaints and pigmentation of gastrointestinal neoplasm or liver disease; from the pigmentation of racial origin and that acquired in hemochromatosis, argyria, acanthosis nigricans, scleroderma and a host of chronic diseases; and from the hypoglycemic reactions of disorders of gastrointestinal motility, hepatic insufficiency and insulinoma. In most of these conditions there are usually sufficiently distinctive features in the clinical picture to make the diagnosis obvious and in some instances more or less specific laboratory procedures are available. In actual practice, there are four clinical patterns in which the diagnosis may remain seriously in doubt without careful screening of adrenocortical function:

1. Patients with established tuberculosis elsewhere in the body whose excessive weakness, gastrointestinal symptoms or pigmentation raises the question of adrenal involvement. This problem may be especially confusing when pulmonary tuberculosis is associated with a low serum sodium concentration.⁴¹
2. Patients with chronic nephritis of the "salt-losing" type who may show a low serum sodium concentration and improve dramatically on a high salt diet.⁴²
3. Patients of dark-skinned races whose cutaneous and mucous membrane pigmentation may be identical with that of Addison's disease.

In such patients a host of common ailments may closely mimic adrenal insufficiency.

4. Patients in whom a prolonged shock-like state follows trauma, surgery or acute illness and in whom primary or secondary adrenal insufficiency is suspected.

In these situations the newer tests of adrenal function are proving invaluable.

TREATMENT OF ADRENAL CORTICAL INSUFFICIENCY AND PREPARATIONS USED*

Preparations

Adrenal Cortical Extract. At present there are several preparations of whole adrenal cortical extract available, practically identical in potency. The majority of such extracts in aqueous form contain activity of the order of 0.1 mg. of cortisone per ml. and 0.03 mg. per ml. of desoxycorticosterone. The active components of these extracts comprise both crystalline and amorphous fractions of adrenal extract. Lipo-adrenal cortex,⁹ a special porcine concentrate, is ten times as active in carbohydrate-regulating activity as most aqueous extracts but contains less of the salt-retaining factors.⁴³ Aqueous extracts, although of relatively low potency, have the advantage of being suitable for any type of parenteral use and particularly for intravenous administration when large quantities of hormone may be needed quickly. Because the action is rapid and of short duration (four to six hours) overdosage is almost unknown.

Desoxycorticosterone Acetate. This synthetic steroid has potent salt and water retaining capacities but in the dosage usually employed there is no effect on intermediary carbohydrate, fat and protein metabolism.⁴⁴ In excess it produces edema, hypertension and hypokalemia and may precipitate heart failure. A flaccid paralysis due to lowered serum potassium levels may result from long-continued excess.⁴⁴ The material is available *in oil* for intramuscular administration, as *pellets* for subcutaneous implantation¹⁷ and in the form of *linguets* or propylene glycol solution for sublingual use. A microcrystalline suspension of trimethylacetate

of desoxycorticosterone in methylcellulose was found to control sodium metabolism satisfactorily for two months following a single intramuscular injection of 60 to 120 mg. For rapid action an aqueous solution containing desoxycorticosterone in solution as the glucoside is available for intramuscular and intravenous use.⁴⁵ Occasional allergic reactions to the vehicle (sesame or peanut oil) are encountered with the intramuscular preparations. By mouth⁴⁶ at least four-fifths of the potency is destroyed whereas in appropriate vehicles sublingually, more than half the potency is preserved.⁴⁷ Through the maintenance of adequate hydration and normal blood pressure desoxycorticosterone has done much toward prolonging the life of patients with Addison's disease.¹⁷

Cortisone Acetate (Compound E). This natural steroid, which has been partially synthesized commercially, has only about one-fiftieth the salt-retaining potency of desoxycorticosterone (Fig. 4) when compared with a maintenance dose of the latter in patients with Addison's disease. While retaining sodium, cortisone acetate will lead to an initial potassium loss, followed by step-wise retention (Fig. 4) due, at least in part, to the binding of potassium with the increase in liver glycogen deposition.

Cortisone acetate preserves carbohydrate stores by decreasing the utilization of carbohydrate and increasing that of fat, as reflected in a transitory rise in fasting ketone bodies and a fall in non-protein R.Q. (Fig. 5),²³ effects not shown by desoxycorticosterone in therapeutic doses. While the rise in fasting blood sugar level is minimal (Fig. 5), the glucose tolerance may be decreased. The anti-anabolic effect of cortisone⁴⁸ may lead to a negative nitrogen balance, although this effect is usually not observed unless amounts in excess of 100 mg. a day are used for periods exceeding three to four days. However, in practical therapeutic situations cortisone often leads to striking improvement in appetite and protein intake so that the over-all effect may be the development of a more positive nitrogen balance.

Certain hematologic effects observed with cortisone are analogous to those found with ACTH in normal human subjects³⁰ but when using saline suspension of cortisone acetate intramuscularly in dosages up to 100 mg. per day the degree of eosinopenia is often unpredictable and may actually be quite minimal. This sluggish eosinopenic response may well be attributable

* We are indebted to the following for the provision of therapeutic agents used in these studies: Dr. E. Oppenheimer, and F. E. Houghton, Ciba Pharmaceutical Products, for desoxycorticosterone acetate; Drs. J. Carlisle and A. Gibson, Merck and Company, for cortisone; Dr. H. Hailman, Upjohn Company, for cortical extracts and lipo-adrenal cortex. Drs. J. R. Mote and J. Hubata, Armour Laboratories, for ACTH.

to slow absorption from the muscle since similar doses by mouth have more striking effects on the eosinophils. (Fig. 6.)

Cortisone acetate is available as a *microcrystalline suspension* in saline (25 mg. per ml.) for intramuscular use and in *tablet form* (25 mg.) for oral

out. In only one instance were pellets extruded after implantation. Wound healing took place by primary intention without keloid formation. The aggregate weights of pellets ranged from 200 to 1,815 mg. The optimum weight was found to lie between 1,000 and 1,500 mg. per implant.

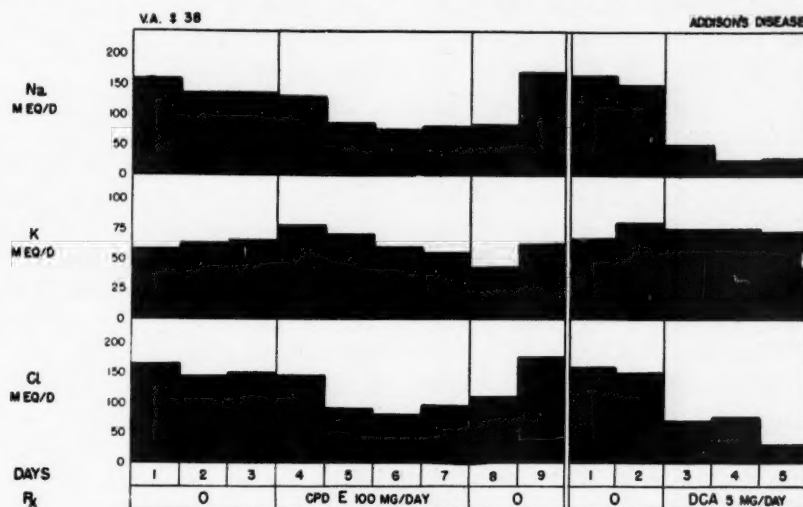


FIG. 4. Comparison of the effects of Compound E acetate and DCA on urinary electrolyte excretion on constant diet.

administration. The *subcutaneous implantation* of pellets has²³ proven useful experimentally but is no longer a method of choice now that the effectiveness of the oral material is well established.³⁷

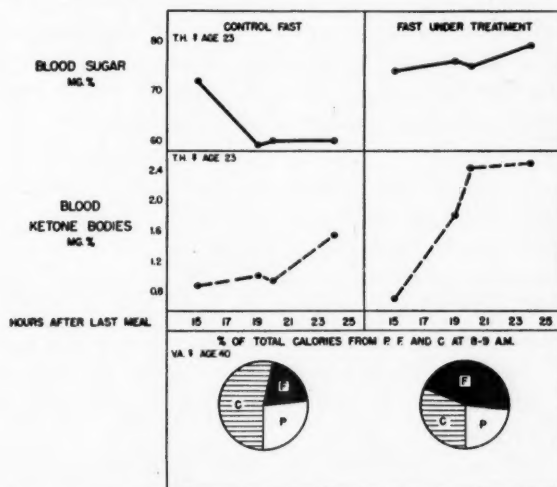


FIG. 5. Effects of Compound E on carbohydrate and fat metabolism in Addison's disease. This material was obtained in collaboration with Dr. Leslie L. Bennett.

Twenty-nine patients received cortisone acetate pellets, approximately 3 mm. in diameter and 0.5 to 3.0 cm. in length. Of these, six received two and three patients three separate implantations, a total of forty implantations being carried

MAY, 1951

The average daily dissolution was found to approximate 1 per cent of pellet weight, as proven by the removal of pellets in five patients after varying periods *in situ*.²³ Thus an implant

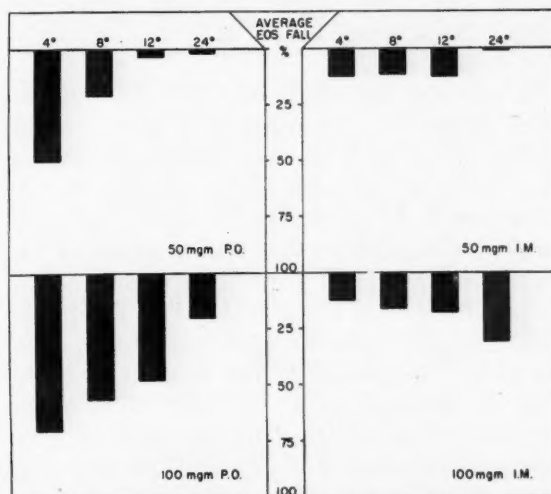


FIG. 6. Eosinophil response to oral or intramuscular administration of cortisone acetate in ten patients with Addison's disease.

of 1 gm. yielded approximately 10 mg. of hormone per day. The clinical effects seen in this series of patients with implanted cortisone were identical in nature with those observed in patients after parenteral injections or oral corti-

sone. Because the duration of clinical effectiveness of one implant appeared to be only four to five months, requiring implantation at least twice a year, this form of therapy was discontinued in favor of oral administration.

Unlike DCA, cortisone acetate is highly active by oral administration. The effectiveness and duration of orally administered material may be demonstrated by following the degree of eosinopenia which is produced. This fall in eosinophils is considerably more marked than that which occurs with intramuscular cortisone and more closely approaches that produced by intravenous administration. (Fig. 6.) Therefore, for rapidity of effect and facility of administration cortisone orally, every six hours, is to be preferred although variations in absorption might alter the effectiveness of a given dosage.

Side effects from cortisone acetate in the doses used for substitution therapy are gratifyingly rare. Only flatulence and mild epigastric discomfort have been encountered with the oral preparation. While allergy to the drug itself probably does not occur, other substances in the parenteral preparation available will occasionally lead to sensitivity reactions. We have encountered one instance of mild purpura with normal platelet count, local irritation at injection sites (including rare ecchymoses) and substernal and pharyngeal burning sensations (which disappeared when tablets of cortisone were substituted).

Dehydrocorticosterone Acetate and Corticosterone. These potent 11-oxysteroids have also been administered to patients with Addison's disease. The early work with dehydrocorticosterone (Compound A) in Addison's disease revealed both a salt-retaining effect and a moderate but definite influence on intermediary metabolism in doses from 40 to 100 mg./day.⁴⁹⁻⁵¹ Essentially similar results, with the additional finding that the slowed frequency of the electroencephalogram of patients with Addison's disease was increased, were obtained by the use of corticosterone (Compound B) by Conn.⁵² He suggested that corticosterone alone, without additional desoxycorticosterone, might provide complete hormonal substitution in Addison's disease.

Management of Adrenal Insufficiency

Addison's Disease. The patient should first be screened carefully for evidence of active tuberculosis, which makes control more difficult and

the use of cortisone in larger doses hazardous. With modern substitution therapy no special dietary regulation is necessary in the majority of patients although asthenia may dictate a high caloric intake with supplementary vitamins for a time. If hypoglycemic attacks are a troublesome feature, small frequent feedings may be a helpful expedient, with special emphasis on a bedtime feeding.

Since about one-third of patients with chronic adrenocortical insufficiency will show near optimal improvement on DCA, it is generally advantageous to begin treatment with this drug alone. Baseline studies of body weight, heart size (7-foot film) and blood pressure are of prime importance before therapy is begun since these will be guides to adequate dosage. DCA in oil can then be given by daily intramuscular injection, commencing with 2 mg. daily and increasing by 0.5 mg. every three to four days up to the early signs of excessive fluid retention. An initial fall in the hematocrit is to be expected since the untreated Addisonian patient is in a state of chronic dehydration; this does not, therefore, indicate overtreatment. Slight periorbital edema or evening swelling of the ankles usually gives the first reliable clue to overdosage; with more marked overdosage headache, hypertension, muscle cramps, muscular weakness and EKG changes (hypokalemia) may occur. The daily dose is then reduced by 0.5 mg. decrements until the weight ceases to increase; at this point one further reduction of 0.5 mg. is made and supplementary sodium chloride is begun in the form of 1.0 gm. enteric-coated tablets, three times a day. The patient may now be discharged from the hospital and final fine adjustments of therapy can be made by appropriate changes in the dose of sodium chloride. At any time the finding of edema, increase in heart size or elevation of the blood pressure above normal (except in rare Addisonian patients with coexistent hypertension) should be heeded as a warning of overdosage.

When the patient has been observed on this type of regimen for a month or more, daily injections may be replaced by pellets. For each 0.5 mg. of DCA in oil required by daily injection, one 125 mg. pellet may be implanted subcutaneously; alternatively, for each 0.3 mg. of DCA by injection, one 75 mg. pellet may be implanted. Beware of narcotics in preparing for this or any other procedure in a patient who is not receiving large doses of cortisone!

If the dose of pellets has been misjudged and signs of overtreatment appear, the daily ration of sodium chloride may be omitted; if this does not relieve the situation, supplementary oral potassium administration may be necessary for some weeks in the form of 4 ml. of a 20 per cent solution of potassium citrate or 0.6 gm. of potassium chloride in enteric-coated tablets every four or six hours. Pellets usually last about eight to ten months and toward the end of this period, or in hot weather, increased amounts of oral sodium chloride will be necessary. The average requirement of desoxycorticosterone acetate (DCA) varied between 1.0 and 3.0 mg. per day in a series of 180 patients with Addison's disease observed in our clinic. On such therapy weight is maintained and blood pressure slowly rises, although not necessarily to normal levels. In many instances normal blood pressure may be achieved only at the expense of accumulating edema. In spite of the maintenance of weight the stabilization of blood pressure and extended survival¹⁷ some two-thirds of Addisonians on desoxycorticosterone acetate are still easily fatigued, irritable, somewhat sluggish in behavior and, as a rule, unable to regain normal weight without edema. A moderate anemia is nearly always present. Many of these remaining abnormalities have been observed to disappear or improve with the use of cortisone.

With the patient established on a satisfactory DCA regimen, it will usually be desirable to encourage a therapeutic trial of cortisone. An adequate trial would consist of 12.5 mg. of cortisone acetate twice a day by mouth for a period of thirty days. This dose does not materially affect DCA requirements. If significant symptomatic improvement occurs, the drug may be continued indefinitely, although half this dosage may be adequate.

Prevention and Treatment of Adrenal Crisis. It must early be impressed upon the patient with Addison's disease that he is perilously vulnerable to trauma and infections. He must be encouraged to avoid fatigue and to follow an adequate diet. Like a diabetic such a patient must be equipped with the drugs and knowledge to deal with illness which may arise when the advice of a physician is temporarily inaccessible. Fortunately, the advent of cortisone has greatly simplified this aspect of treatment.

Every patient, whatever his routine therapy, should have in his possession a vial of DCA in oil, a vial of cortisone acetate suspension and a

supply of cortisone tablets. He should be schooled to take, at the first symptoms of a respiratory infection or malaise of any sort, 25 mg. of cortisone orally four times a day. For more severe illness, especially if associated with nausea, vomiting or fever, 50 mg. twice daily by intramuscular injection should be advised. In addition, patients likely to be isolated from medical care may profitably carry with them a supply of an antibiotic for emergency use. However, both patient and physician must appreciate the gravity of any but the mildest illness and agree to hospitalization and close medical supervision as soon as possible.

In patients seen for the first time in adrenal crisis, or in whom frank crisis has been precipitated by intercurrent illness, more energetic measures are necessary. DCA in oil, 10 mg., and cortisone acetate, 100 mg. intramuscularly, and 20 to 30 cc. of aqueous adrenal cortical extract, intravenously, should be given without delay. Intravenous fluid therapy is directed toward restoring sodium chloride deficit and extracellular fluid volume and toward combatting the hypoglycemia. For this purpose 1,000 cc. of 10 per cent dextrose in saline, containing 20 to 30 cc. of aqueous extract, is usually adequate during the first twelve hours (although larger amounts may be necessary if dehydration is severe), to be followed by 1,000 cc. of 10 per cent dextrose in water during the second twelve hours if sweetened fruit juices and milk cannot be given by mouth. When grave hypotension dominates the picture, phenylephrine hydrochloride (neosynephrine) may be given as described under management of bilateral adrenalectomy. If available, human albumin (25 to 50 gm.) may be infused intravenously, or alternatively, a unit of whole blood or 1 or 2 units of plasma will help to maintain blood volume and to protect the patient from water intoxication. Cortisone acetate should be continued in doses of 50 to 75 mg. intramuscularly every six hours until the patient is out of danger. Even in the absence of obvious infection antibiotic therapy should be instituted prophylactically from the time the patient is first seen.

If cortisone is not available, adrenal cortical extract may be substituted. In mild intercurrent illness 5 cc. of aqueous extract (or 1 cc. of Upjohn's lipo-adrenal cortex) may be given intramuscularly every six or eight hours. In frank crisis the patient should receive at least 100 cc. of aqueous extract intravenously during

the first four hours and 5 cc. intramuscularly for every hour of critical illness.

Clinical Experience with Cortisone Therapy. The earlier findings in the investigation of the use of cortisone in adrenal insufficiency^{23,29,53,54} have been expanded. The addition of cortisone to the therapeutic DCA regimen has brought about remarkable changes in the majority of forty-eight patients with Addison's disease who have received cortisone to date. Of these thirty patients have been treated continuously with cortisone for periods ranging from three months to two years. All these patients have received intramuscular injections of cortisone acetate in saline suspension at one time or another for varying periods. Twenty-nine patients received subcutaneous implantations of cortisone acetate pellets²³ and twenty-four patients have been carried on oral cortisone. One injection a day, which need not exceed 12.5 mg., or from 6.25 to 12.5 by mouth twice a day, appears to afford highly satisfactory replacement.

The use of small doses (6.25 to 25 mg. per day) of cortisone as replacement therapy in patients with Addison's disease has been remarkably free from undesirable effects. Indeed, the only clear-cut reaction of this sort has been evidence of mental excitement which occurs not infrequently during the early days or weeks of treatment. This manifestation seems almost always to pass off spontaneously as administration of the drug is continued. In one patient who showed evidence of emotional instability before therapy frank psychotic manifestations appeared following 25 mg. per day for six weeks but regressed when the dosage was reduced to 12.5 mg. per day. Experiences of this sort underline the desirability of seeking the minimum dose of cortisone which will induce optimal improvement.

All patients have shown a marked increase in appetite, accompanied with weight gain in eighteen out of twenty-one as shown in a series on 25 mg. of cortisone acetate per day for six months or more. (Table iv.) A decreased need for sleep is characteristic, accompanied with a definite euphoria and a feeling of well being. The skin becomes warmer. Hair growth is increased both in the sexual areas and on the scalp. The pigmentation of the skin, while sometimes increased at the site of implantation of cortisone pellets,²³ shows an over-all decrease on prolonged therapy. Acne has not been observed. Muscular strength and work capacity have shown dramatic improvement and along with an associated in-

creased aggressiveness may enable the patient on cortisone therapy once again to resume normal activities.

With these striking clinical changes measurable physiologic effects are few. Eosinophils are depressed only little on 25 mg. of cortisone

TABLE IV
WEIGHT CHANGES ON CORTISONE ACETATE THERAPY IN
TWENTY-ONE PATIENTS WITH ADDISON'S DISEASE

	Weight (kg.)		
	Before	After	Change
Mean.....	55.4	60.5	+5.1
Range.....	(38-79)	(43-82)	(0 to +12)

acetate per day. While there is no marked rise in fasting blood sugar, the tendency toward hypoglycemia is practically abolished. The anemia found so commonly in Addison's disease is markedly improved. Eighteen of twenty-one patients on cortisone for more than six months showed improvement in hematocrit levels ranging from 2 to 13 ml. of packed red cells per 100 ml. of blood while two showed no change. The mean rise was 5.5 ml. per 100 ml. of blood. (Table v.) The total serum protein rose 0.3-

TABLE V
CHANGES IN HEMATOCRIT FOLLOWING CORTISONE ACETATE
DAILY IN ADDISON'S DISEASE
TREATED SIX MONTHS OR MORE

Sex	No.	Mean Hematocrit Before Treatment (%)	Mean Hematocrit After Treatment (%)	Mean Rise (%)
Female.....	14	35.1	40.4	5.4
Male.....	6	35.4	43.5	6.3

1.1 gm. per cent in fifteen of the twenty-one patients and appeared to be characteristic of continued cortisone therapy in most patients with Addison's disease. One patient failed to show a change and three demonstrated a moderate decrease of 0.3 to 0.5 gm. per cent.

The most consistent change is the return of the slowed electroencephalogram to normal rates on doses of 25 mg. of cortisone acetate per day given over a period of months. Twenty-five of twenty-six patients with adrenal insufficiency

demonstrated definite improvement on treatment with cortisone acetate. The criteria employed were changes in two components of the EEG: (1) the predominant frequency, (2) the lowest frequency. Results of an analysis of ten patients treated with 25 mg. of cortisone acetate per day for more than six months are shown in Figure 7. It will be noted that such therapy raises the frequency toward, but not necessarily up to, the normal level. Electroencephalographic improvement regularly followed oral or intramuscular administration of 12.5 to 25 mg. of cortisone daily, or equivalent dosage in the form of pellets. While the data indicate that the effect on the electroencephalogram is a function of time as well as dose, improvement has been observed following a single intramuscular injection of 100 mg. of the drug.

Part I of the Robinson-Kepler-Power water test³² was performed before and during cortisone therapy in fourteen patients with Addison's disease. The patients received with their usual doses of desoxycorticosterone acetate supplementary cortisone either orally, by intramuscular injection or in the form of subcutaneous pellets. In all patients the control water test was grossly abnormal. The effects of cortisone on this test were obviously related to dosage level. Nine patients received daily doses of 25 to 100 mg. per day (average 80 mg. per day) for periods varying from 1 to 120 days (average 10 days). Of this group seven showed complete reversal of the test to normal and the remaining two marked improvement. On the other hand, of tests in seven patients who received 12.5 mg. or less per day (average 9 mg. per day) for 8 to 120 days (average 85 days) only one showed complete reversal, one improved and the remaining five were unchanged. It would appear that in the majority of cases the reversal of the water test requires larger doses of cortisone than the daily ration (12.5–25 mg.) which, in combination with conventional doses of DCA, is adequate to induce optimal symptomatic improvement in patients with Addison's disease.

The sodium-retaining effect of cortisone in dosages below 100 mg. per day is insufficient to obviate the need for added salt or desoxycorticosterone acetate. The combination of desoxycorticosterone (1.0 to 2.0 mg.) and cortisone acetate (12.5–25 mg) daily appears to constitute the treatment of choice.

An additional effect of cortisone has been the reversion of the abnormal four-hour ACTH and

epinephrine tests toward normal in seven patients treated with cortisone. (Table III.) An illustrative case is presented:

H. W. (P.B.B.H. No. 5B36), a thirty-four year old clerk with an established history of Addison's disease extending over a period of six

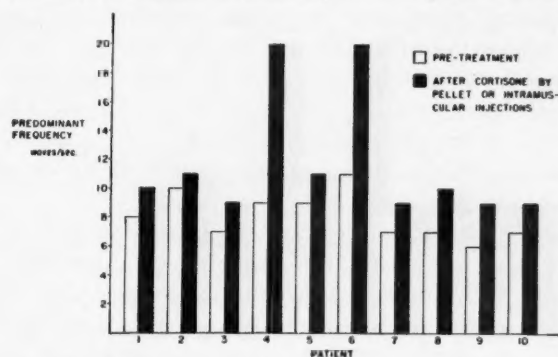


FIG. 7. Effect of cortisone acetate on the electroencephalogram in Addison's disease.

years, had been maintained on desoxycorticosterone pellets with supplementary adrenal extract during intercurrent infections. Routine screening tests produced the following results: four-hour epinephrine test, 15 per cent increase in eosinophils; four-hour ACTH test, 16 per cent eosinophil fall; *impression*: Addison's disease.

In May, 1950, the patient received 375 mg. desoxycorticosterone and 1,077 mg. cortisone by pellet implantation, later supplemented by intramuscular cortisone, 12.5 mg. per day. Upon return to the hospital in November, 1950, further study showed the following responses: four-hour epinephrine test, 72 per cent eosinophil fall; four-hour ACTH test, 69 per cent eosinophil fall; forty-eight-hour ACTH test, 44 per cent eosinophil fall and 6.5 mg. increase in 17-ketosteroids per twenty-four hours; *interpretation*: Essentially normal four- and forty-eight-hour tests in a previously well established case of Addison's disease treated with cortisone.

The use of cortisone acetate in the management of patients with co-existing Addison's disease and diabetes mellitus has proved particularly helpful in stabilizing the blood sugar and reducing the ill effects of recurrent hypoglycemia such as disorientation, headache and mental negativism. Two such cases have done well on treatment with cortisone for one year.

K. H. (P.B.B.H. No. 5B877), a forty-two year old housewife and a diabetic for seventeen years, required 30 units of PZI and 10 units CZI for adequate control. Two years before admission she had noted pigmentation of the gums

and six months before admission loss of vitality, weakness and frequent attacks of hypoglycemia. Her insulin requirement fell to 16 units NPH50 insulin and 4 units CZI. A weight loss from 140 to 117 pounds occurred. The diagnosis of Addison's disease was made on the basis of clinical signs and an acute vascular collapse and was confirmed by a 17-ketosteroid excretion of 2.4 mg. per day and a rise of 6 per cent in the circulating eosinophils on a four-hour ACTH test. The electroencephalogram was mildly slowed, fasting blood sugars ranged from 79 to 320 mg. per cent.

Treatment consisted of implantation of three 125 mg. pellets of DCA and 234 mg. of cortisone pellets. A second implantation of 1,075 mg. of cortisone acetate pellets was carried out four months later. After five months 12.5 mg. of cortisone acetate orally twice a day was begun. While there was a decrease in the severity of hypoglycemic attacks and an increase in strength and appetite after the implantation of cortisone pellets, this was even more marked following the larger daily amounts of cortisone orally. In both instances the insulin requirement increased so that the patient now takes 36 units of NPH50 insulin on the same diet. The urine sugar varies from 1 to 2 plus. This represents a diabetic picture analogous to that present before the onset of Addison's disease. The patient has had a complete return of strength, endurance, vigor and appetite with a weight gain of 16 pounds. Her pigmentation has decreased noticeably.

J. H. (P.B.B.H. No. 5A785), a thirty-five year old male, developed Addison's disease thirteen years ago and diabetes four years later.⁶⁵ He had required between 8 to 12 units of insulin daily and three 125 mg. pellets of desoxycorticosterone annually with variable amounts of lipo-adrenal cortex (1-2 mg. per day intramuscularly). An erratic and often excessive intake of carbohydrate in an attempt to counteract the frequent occurrence of symptoms of hypoglycemia led to wide swings in fasting blood sugar (80 to 415 mg. per cent). One implantation of cortisone acetate pellets weighing 968 mg. improved the patient greatly. Now, on 12.5 mg. of cortisone orally once a day in addition to three 125 mg. DCA pellets, the patient requires 16 units of NPH50 insulin, takes in 2,500 calories and has regained his strength and 30 pounds in weight. Hypoglycemic attacks are very rare and in contrast to previous ones are milder and

shorter. Headaches, formerly a frequent occurrence, no longer recur. Cutaneous pigmentation has lightened considerably and there has been marked growth of body hair, both in the sexual areas and over the temples. He is actively pursuing his business interests for the first time in over ten years.

Secondary Adrenal Cortical Insufficiency. In this condition additional glandular deficiencies co-exist with adrenal cortical insufficiency. While treatment does not differ significantly from that of primary insufficiency, optimum symptomatic improvement requires specific replacement therapy for the associated hypothyroidism and hypogonadism, which may affect the requirements of adrenal cortical hormone. For example, thyroid therapy will increase the basic requirement of 11- and 17-oxysteroids while testosterone or estrogens, by producing salt and water retention, reduce the basic requirements for desoxycorticosterone. The characteristic tendency of patients with secondary adrenal cortical insufficiency to develop hypoglycemia makes the use of cortisone or similar carbohydrate-regulating factors of peculiar importance to their proper management.

R. J. G. (P.B.B.H. 5A755) was well until 1939 when, at the age of twenty-five, following the miscarriage of a six months' fetus, she suffered a uterine hemorrhage which necessitated hysterectomy. She remained prostrated thereafter, with nausea, vomiting, diarrhea and hypotension until the institution of therapy with DCA and eschatin. From 1939 to 1948 she received, on the average, three 125 mg. pellets of DCA per year plus a daily ration of 5 cc. of eschatin (without which hypoglycemia and prostration were inevitable) and 60 mg. of thyroid extract. In spite of this therapy she remained weak and lethargic and lived a semi-invalid existence punctuated by more or less severe adrenal crises precipitated several times each year by intrinsically minor illnesses, such as upper respiratory infections. During this period her average weight was 47 kg. and her hematocrit remained about 33. For the past two years she has received cortisone either in the form of pellets or by daily intramuscular injection with an average daily dose of 10 mg. per day. During this period there has been a dramatic return of physical strength and mental vigor, along with return of libido. Slight growth of hair appeared in the axillas and on the legs. Her weight has risen to 54 kg. and her hematocrit is now 40.

Cortisone improved the previously slowed electroencephalogram but it was interesting to note that this did not become normal until the daily dose of thyroid extract was raised to 120 mg. The water test is now within normal limits.

In contrast to the primary type, secondary adrenal cortical insufficiency may be managed successfully with ACTH therapy. This is most advantageously used in the preoperative preparation of patients for pituitary surgery.¹¹ While the prolonged use of ACTH might provide adequate adrenal cortical hormone production as maintenance therapy, this method of treatment has not yet received adequate trial.

Treatment during Bilateral Adrenalectomy. The removal of both adrenal glands poses a problem in management of the adrenal cortical insufficiency which develops immediately under the stress of major surgery and of the chronic adrenal cortical insufficiency which follows. The type of adrenal cortical replacement therapy to be used under such circumstances may be illustrated by recent experiences in seven patients who have undergone bilateral adrenalectomy for hypertension.⁶ A forty-eight-hour ACTH test is the final preoperative study, begun on the third day before surgery in order to take advantage of the increase in circulating adrenal cortical steroids which this provides for the operation. The ACTH is continued during the next twenty-four hours up to the time of operation (10 to 25 mg. every six hours); 100 mg. of cortisone acetate is given intramuscularly twelve hours before surgery, and an additional 50 mg. two or four hours preoperatively. The slow absorption from the intramuscular site provides a constant and prolonged level of circulating cortical steroids. Continuous spinal anesthesia appears preferable to ether.

During the operation aqueous adrenal cortical extract is given slowly intravenously in 5 per cent dextrose solution in a total amount of 100 to 200 ml. over the three and one-half to four-hour operative period. This infusion is continued postoperatively until the entire 100 to 200 ml. of extract has been infused. Hypotension, which not uncommonly develops acutely during the operative or immediate postoperative period, usually responds well to phenylephrine hydrochloride (neo-synephrine). This may be administered in doses of 1.0 mg. as a single slow intravenous injection or, when hypotension is more prolonged, 10 mg. of the drug may be added to 1,000 cc. of dextrose or saline solution

and given by slow intravenous drip. Refractory hypotension after bilateral adrenalectomy may respond dramatically to whole blood transfusion even though blood loss during surgery has been minimal.

The evening following operation cortisone acetate, 50 mg., is given intramuscularly and continued every eight hours at that dosage. Depending upon the general condition of the patient, the dose of cortisone acetate is reduced to 50 mg. every twelve hours and then to 25 mg. every twelve hours so that by the sixth or seventh day postoperatively the patient is receiving 25 mg. of cortisone intramuscularly twice daily. Near the end of the second postoperative week this is further reduced to a level of 12.5 mg. twice daily and can then be administered orally. During the immediate postoperative period the intake of sodium chloride is kept at a level of 6 to 8 gm. per day; this, together with the daily ration of cortisone, is usually sufficient to ensure satisfactory electrolyte balance. As the cortisone is reduced to 12.5 mg. twice daily, supplementary DCA is likely to be necessary in daily amounts of 1 to 2 mg. intramuscularly. This dosage may be regulated to maintain the basal blood pressure level at which each individual patient enjoys an optimal sense of well being. This is found to be characteristically higher than the accepted normal range in the previously hypertensive patient.

SUMMARY AND CONCLUSIONS

The advent of ACTH and cortisone has opened a new chapter in the diagnosis and treatment of adrenal cortical insufficiency. In specific stimulation of the gland by ACTH we have for the first time achieved the goal of testing adrenocortical reserve. No longer must accurate diagnosis await the development of advanced disease. In the realm of therapy we need not be limited to the repair of the disordered electrolyte balance by means of diet and desoxycorticosterone administration, measures which, while protecting the hypoadrenal patient against dehydration and shock, yet all too often leave him more or less crippled by residual metabolic defects. As shown by these preliminary studies, cortisone, by filling this gap in therapy, has made it possible to restore the great majority of patients to an active life. Thus through the development of both a specific adrenal stimulant and adequate amounts of potent synthetic adrenal steroids, adrenal cortical insufficiency

is no longer the obscure and deadly disease of the past, but a state to be frequently anticipated, easily recognized and successfully treated.

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Hyperadrenocorticism*

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EXCESSIVE secretion of adrenal steroids produces variegated clinical pictures. When marked physiologic and anatomic changes result, the condition is usually designated as adrenogenital syndrome or Cushing's syndrome. However, less clearly defined allied disorders are encountered much more frequently. In instances of severe stress rarely is the clinical picture of Cushing's syndrome produced although a few of its manifestations may appear.

In this paper, following a brief discussion of normal adrenal physiology, various clinical entities of chronic hyperadrenocorticism and allied disorders are described.

FUNCTIONS OF THE ADRENAL CORTEX AND ITS STEROIDS

The adrenal cortex secretes steroids which directly or indirectly exert many effects throughout the body. They play an important role (1) in the regulation of electrolyte and water balance, (2) in somatic growth and in the development and function of sex structures and (3) in the metabolism of carbohydrates, proteins and fats. The primary and subsidiary functions are so numerous and of such a nature that some of the effects supplement one another while others are antagonistic.

Elucidation of the precise action of adrenal steroids has been handicapped by a lack of knowledge of just which steroids the glands of normal and abnormal individuals secrete. Approximately thirty steroids, with a predominance of 17-hydroxycorticosterone,¹ have been isolated from animal adrenals and more than forty have been recovered from human urine, but it is not known in how many instances the chemical structure was altered in the process of isolation or, in the case of urine studies, by other portions of the body. Nevertheless, studies with some of these steroids have yielded information of aid in understanding characteristics of hyperadrenocorticism.

11-Desoxycorticosterone causes a marked re-

tention of sodium, chloride and water, and urinary excretion of potassium and phosphorus. Large doses of this steroid produce hypertension when there is no restriction of sodium chloride intake. It has only a mild and indirect effect (e.g., via pituitary inhibition and improved gastrointestinal function) on carbohydrate metabolism. 17-Hydroxy-11-desoxycorticosterone has an action similar to 11-desoxycorticosterone in the few studies conducted thus far. Neither compound has an -O or -OH group attached to C₁₁. There is no proof that either of these steroids is secreted by the adrenal.

The adrenal exerts an androgenic effect. It stimulates the growth of body hair, especially axillary and pubic, growth of clitoris (? normally) and increases muscle mass, strength and general somatic growth. Steroids with the chemical structure of androgens, e.g., adrenosterone and 11-hydroxyisoandrosterone, have been isolated from the adrenal, and similar steroids (androsterone, etiocholan-(3 α) ol-(17)one and dehydroisoandrosterone) have been found in the urine of normal and castrate men and women. None of these steroids is as androgenic as testosterone. The urine of normal women contains approximately two-thirds as much 17-ketosteroid as that of men. With certain diseases of the adrenal, discussed later, there is a quantitative and perhaps a qualitative alteration in the urinary steroid pattern.

Steroids exerting the greater influence on carbohydrate metabolism are corticosterones with an -O or -OH group attached to C₁₁; the effect is greatest with an -OH group also at C₁₇. Examples of the glucosteroids are corticosterone, 11-dehydrocorticosterone (Kendall's Compound A), 17-hydroxycorticosterone (Kendall's Compound F), and 17-hydroxy-11-dehydrocorticosterone (Kendall's Compound E, cortisone). These compounds antagonize protein anabolism and indirectly promote deamination of amino acids and their conversion to carbohydrate. Cortisone has been studied more

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than the others.^{2,3} It markedly suppresses glucose utilization, which may lead to gluconeogenesis.⁴ It lowers the threshold for glucose excretion, decreases the glutathione content of the blood and causes inactivation of -SH groups. It increases the mobilization and utilization of fat. It causes an increased urinary excretion of nitrogen, creatine, uric acid and uropepsin. It increases gastric pepsin, gastric mucoprotein, gastric mucoprotease, serum peptidase, liver and kidney arginase. It decreases histamine and histamine sensitivity and increases histaminase. It interferes with many antigen-antibody reactions. It inhibits hyaluronidase, decreases the number of fibroblasts and increases the number and activity of macrophages. It provokes reticulocytosis, erythrocytosis, neutrophilia, eosinopenia and lymphopenia.

Cortisone sometimes produces retention of sodium, chloride and water, but more often, particularly after prolonged administration, it promotes their excretion, probably by antagonizing antidiuretin and desoxycorticosterone. It causes the excretion of potassium, calcium and phosphorus. Occasionally, it produces hypokaliemic hypochloremic alkalosis. Weakness and other manifestations of disturbed muscle function may be observed. Cortisone increases the alpha rhythm and the number of beta waves. It increases mental acuity and causes restlessness. With the administration of small doses of cortisone there is a decrease in the excretion of 17-ketosteroids due to inhibition of adrenocorticotrophin secretion but with large doses there is an increase because of conversion of cortisone to a 17-ketosteroids. While there is an increase in cortisone and 17-hydroxycorticosterone in the urine with cortisone treatment,⁶ less than 5 per cent of the cortisone appears in the urine.

17-Hydroxycorticosterone, although studied much less intensively than cortisone, has been found similar in action; its effects on carbohydrate metabolism are more potent. 11-Dehydrocorticosterone, directly or indirectly, may promote the development of obesity.⁶

Progesterone and estrone have been isolated from adrenal tissue and from the urine of normal and castrate men and women. These steroids affect predominantly the genital structures, but they also influence water and electrolyte balance.

In summary, the various steroids isolated from the adrenals differ in the responses that they produce, but most of them exert, in some man-

ner, an effect on water and electrolyte balance, carbohydrate, fat and protein metabolism, and growth and development.

The rate of function of the adrenal cortex is markedly dependent upon the pituitary. The latter secretes adrenocorticotrophic hormone (ACTH) which stimulates the adrenal to secrete steroids in increased amount.^{7,8} Injections of ACTH produce a pronounced effect on water and electrolyte balance, androgenesis, gluconeogenesis and other effects produced by cortisone. It has been supposed that three different types of steroids, described earlier, are necessary to produce these effects. However, 17-hydroxycorticosterone, in addition to exerting a pronounced gluconeogenic effect, promotes changes in water and electrolyte balance similar to those of desoxycorticosterone.⁹ Most if not all¹⁰ of the steroid isolated from the adrenal vein after ACTH administration is 17-hydroxycorticosterone. ACTH also causes an increase in this steroid in the urine² along with an increase in 17-ketosteroids and an increase in cortisone, according to some investigators.⁵

It is difficult to interpret some aspects of steroid metabolism since there may be interconversions of many of these compounds. For example, cortisone presumably can be changed to 17-hydroxycorticosterone⁵ and to 17-ketosteroids;² on perfusing isolated adrenal glands 11-desoxycorticosterone can be converted to corticosterone¹¹ and 17-hydroxydesoxycorticosterone to 17-hydroxycorticosterone.¹² Examples of "pure" adrenogenital syndrome suggest that, at least on occasions, the adrenal may produce an excess of steroids that have an androgenic action but no gluconeogenic effect. Moreover, the qualitative variation of adrenal function is illustrated by the fact that the androgenic activities of the adrenals, as indicated in girls by the growth of sexual hair, are not manifested until the age of puberty although there is no significant change in the electrolyte and carbohydrate regulating activity of the gland at this time. Although children produce normal adult amounts of urinary corticosteroids almost from birth, they excrete very little 17-ketosteroid until the pre-menarché interval. Thus there appears to be a temporal quantitative difference in the relative amounts of steroids secreted or in their effectiveness.

The zone in the adrenal cortex in which different steroids are manufactured has not been proved. It has been postulated that the andro-

gens are elaborated by the zona reticularis, the glucosteroids by the zona fasciculata and the mineralo-corticoids by the zona glomerulosa. With hypophysectomy there is less atrophy of the zona glomerulosa than of the other zones and relatively less impairment of water and electrolyte balance.

Whether adrenocorticotrophin is the only pituitary hormone which stimulates the adrenals is not known. On the basis of clinical observations it has been postulated that the luteinizing hormone might stimulate androgenic function, but when pure luteinizing hormone is given to hypophysectomized rats no stimulation of the adrenal is observed. The amount of ACTH secreted is governed chiefly by (1) the rate of utilization of adrenal steroids¹³ and (2) autonomic stimuli to the adrenal medulla.¹⁴ With a decrease in the concentration of corticosteroids in the body the pituitary is stimulated to secrete more ACTH, which attempts to supply more steroids by stimulating the adrenal cortices. Innumerable chemical compounds, especially epinephrine, and diseases increase the demands for ACTH by increasing the rate of utilization of the corticosteroids. When adequate doses of cortisone are given, there is no evidence of increased ACTH production in severe stress.

With the administration of an excess of certain steroids, e.g., cortisone, desoxycorticosterone and testosterone, the release of ACTH is inhibited and the adrenal becomes atrophic, especially the zona fasciculata and reticularis.

Epinephrine is required when rapid cortical activation is necessary. Neurogenic and/or psychogenic stimuli go to the hypothalamus and from this area impulses are transmitted through the autonomic nervous system to the adrenal medulla causing secretion of epinephrine. This hormone stimulates the pituitary directly to secrete ACTH. Thus the nervous system is important in causing secretion of epinephrine, but not for epinephrine's effectiveness on ACTH release from the pituitary.^{12,14}

ADRENOGENITAL SYNDROME

The adrenogenital syndrome is produced by the excessive production of androgens from the adrenals. Other adrenal steroid functions may be increased, decreased or remain unchanged. The most pronounced disturbances observed clinically consist of (1) alterations in the structure and function of the genitals and (2) manifestations of hyperanabolism. The net results

vary considerably in different individuals being influenced particularly by (1) the quantity and type of steroid, (2) the age at onset and (3) the sex.

As with many other endocrinopathies the younger the individual the more outstanding do the clinical disturbances tend to be. When the disease begins congenitally it produces abnormalities in sex differentiation which have been excellently described and illustrated by Wilkins.¹⁵ Pronounced effects on skeletal growth occur when it appears before the epiphyses have closed. When developed in "pure form," there is a marked increase in muscle mass and strength, body hair and clitoral size. Abnormalities in menstruation are common. Males may have precocious sex development and testicular atrophy; in rare instances of hyperfunction of the adrenal cortex of males, especially when there is an increase of estrogen, feminization occurs.

With the adrenogenital syndrome there is either bilateral hyperplasia of the adrenal cortices or a neoplasm. The latter often is malignant and tends to metastasize to the liver, lungs and bone; invasion of the renal veins and vena cava is not uncommon. A large number and a wide variety of crystalline steroids have been isolated from the urine of patients with hyperadrenocorticism. The chemical pattern varies almost as much as the clinical syndrome. There is no one steroid or combination that is always present in any one entity. Probably most of the steroids are modified in some way before they are excreted. For example, dehydroisoandrosterone which is often excreted in increased quantities in the adrenogenital syndrome, can be excreted as such, as androsterone, or as etiocholanolone; these steroids vary considerably in their androgenicity. In the adrenogenital syndrome there is usually an increase in the 17-ketosteroids and androgens in the urine although not always. Occasionally, both in males and females, there is an increased estrogen excretion. In the "pure form" of adrenogenital syndrome normal values are usually obtained for the urinary excretion of 11-oxycorticosteroid-like substances¹⁶ and the glucose, insulin and glucose-insulin tests are normal. Indeed, there usually is no evidence of impairment of the desoxycorticosterone-like function or the gluconeogenic action; exceptions, however, do occur and are discussed subsequently.

It has not been established where the primary

disturbance exists in the adrenogenital syndrome. The observations of some investigators¹⁷ have suggested that the condition results not from an abnormal pituitary stimulation of the adrenal but from an abnormal adrenal response to a normal pituitary.

Adrenogenital Syndrome in Females

Since there is considerable difference in the clinical picture and in its therapy depending on whether the condition is congenital or develops later, a separate discussion is given.

Congenital Adrenal Hyperplasia: (Pseudohermaphroditism). This is the commonest clinical adrenal disorder in childhood. The disease frequently occurs in several siblings, the males developing precocious puberty and other changes, designated macrogenitosomia precox and described later. The hyperandrogenism apparently begins to manifest itself in the embryo between the third and fifth month. Normally during this interval in the female the wolffian duct disappears and from the müllerian duct are formed the fallopian tubes, uterus and vagina. With the elongated growth of the anterior wall of the vagina the latter develops an opening of its own and the urogenital sinus, from which the wolffian and müllerian ducts originally branched, disappears. However, in the adrenogenital syndrome the excess of androgens causes the müllerian duct to continue to open into the urethra forming a persistent urogenital sinus, as in the male.

At birth the clitoris is enlarged and has a groove on its ventral surface. On the posterior portion is a small opening of a urogenital sinus. The clitoris resembles a hypospadiac penis. It is bound ventrally by fibrous cords. The labia majora are hypertrophied. By means of urethroscopic examination and lipiodal vaginograms usually the vagina is demonstrated to empty into a small urogenital sinus resembling a urethra; occasionally the sinus is much larger. The ovaries, tubes and uterus may appear normal or atrophic. The adrenals are usually enlarged two or three times normal size. There is diffuse hyperplasia in the cortices and most of the cells may resemble those of the reticular zone; other zones of the adrenal tend to be diminished.

After birth the infants show striking general manifestations of hyperandrogenism, especially the hyperanabolic character. There is rapid skeletal growth and epiphyseal ossification; indeed, they may be far advanced for the age of

the patient. However, epiphyseal fusions occur early and the eventual height tends to be shorter than the average normal. Muscle mass increases rapidly and there is extraordinary strength and stamina. Axillary and pubic hair develop in the first few years; acne also appears. The clitoris continues to enlarge (Fig. 1), becomes a prominent erogenous zone and is frequently erected. By adolescence the patient is apt to be short. The arms and legs are short and the trunk is relatively elongated. She is very muscular with broad shoulders and narrow hips. She has a deep voice and coarse black hair on the extremities, face, abdomen and sometimes on the chest. Development of the breasts and menstruation are impaired. The excretion of 17-ketosteroids is several times normal.

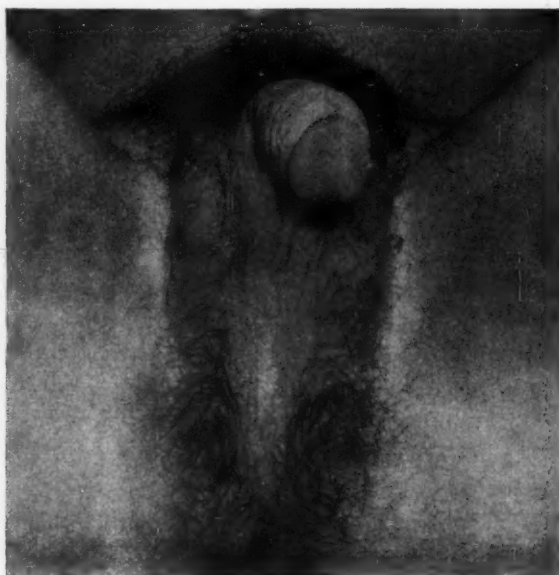
Adrenogenital Syndrome Appearing Post-natally. When virilization appears between birth and the tenth year, it is almost always due to an adrenal tumor. The masculinization begins in the first few months and progresses rapidly. The clinical manifestations are similar to those of the congenital variety, except that the embryonic abnormalities of sex differentiation found in the congenital type are absent; there is normal vulvar configuration and separate openings of the urethra and vagina. The clitoris is not as large as in the congenital type. The adrenal tumor may be small and impalpable or it may extend below the level of the umbilicus. The neoplasm is prone to be malignant and metastasize to the liver, lungs and bones; hypertension rarely occurs. There is usually greater excretion of the 17-ketosteroids especially of the beta fraction than in the congenital type.

Adrenogenital Syndrome in Adolescents and Adults. The adrenogenital syndrome occurs in adolescents and adults more frequently than in childhood, yet it is still a rare disease. It may be associated with carcinoma of the adrenal, but more often there is bilateral diffuse hyperplasia; occasionally along with an adenoma.

The patient may be tall, short or of normal height depending upon the age of onset of the disease. While the hyperandrogenism increases the rate of vertical growth, it also promotes closure of epiphyses thereby preventing further increase in height. The patients are strong, have prominent muscles and a general masculine configuration. (Fig. 2.) Coarse black hair may be over the entire body, but especially on the face, extremities and lower abdomen. The thyroid cartilage and laryngeal structures are



1A



1B

FIG. 1. Adrenogenital syndrome in a girl aged eight, due to congenital adrenal hyperplasia (female pseudohermaphroditism). Height 57 inches; weight 91 pounds. A, note masculine configuration and pubic hair; B, note markedly enlarged clitoris, bound ventrally by fibrous cords; sulcus resembles that of hypospadiac penis; small opening into urogenital sinus. (From BISSELL, G. W. and WILLIAMS, R. H. *Ann. Int. Med.*, 22: 773, 1945.)

enlarged and the voice is deep. The breasts may be small, normal or large. The labia majora and clitoris are enlarged. Libido may be increased, normal or decreased. Menses are infrequent and scanty. The urinary excretion of 11-oxycorticosteroid-like substances is normal whereas the 17-ketosteroid excretion is increased markedly with a neoplasm.

Differential Diagnosis. Congenital adrenal hyperplasia (pseudohermaphroditism) must be differentiated from intersexuality (hermaphroditism).^{*} In intersexuality there is a marked hereditary tendency but the disease ordinarily does not appear in siblings; with congenital adrenal hyperplasia the situation is reversed. When there are testes or ovotestes instead of ovaries, the external genitalia may be similar to that of the pseudohermaphrodite. However, a normal 17-ketosteroid excretion and the lack of development of secondary sexual characteristics help distinguish the conditions; occasion-

ally exploratory operation and biopsy are necessary. Bilateral hyperplasia, as the cause of hyperandrogenism, may be differentiated from a neoplasm by the facts that with the latter there is usually (1) more rapid development of virilization, (2) larger excretion of 17-ketosteroids and (3) a palpable tumor. However, perirenal air insufflation or exploratory laparotomy may be indicated to establish the diagnosis; the choice varies in different clinics (the author usually prefers laparotomy).

Homologous sexual precocity in the absence of metabolic symptoms does not occur as a result of adrenal cortical hyperfunction. With precocious sexual development of the feminine type the genitalia are normal and there is development of the breasts and vagina in conjunction with the appearance of axillary and pubic hair. Moreover there are no evidences of virilism or hyperandrogenism. The 17-ketosteroid excretion is not significantly elevated.

Virilization is produced by an arrhenoblastoma but not below the age of fifteen.¹⁵ The 17-keto-

^{*} For detailed discussions, the reader is referred to the excellent monographs of Young¹⁸ and Wilkins.¹⁵

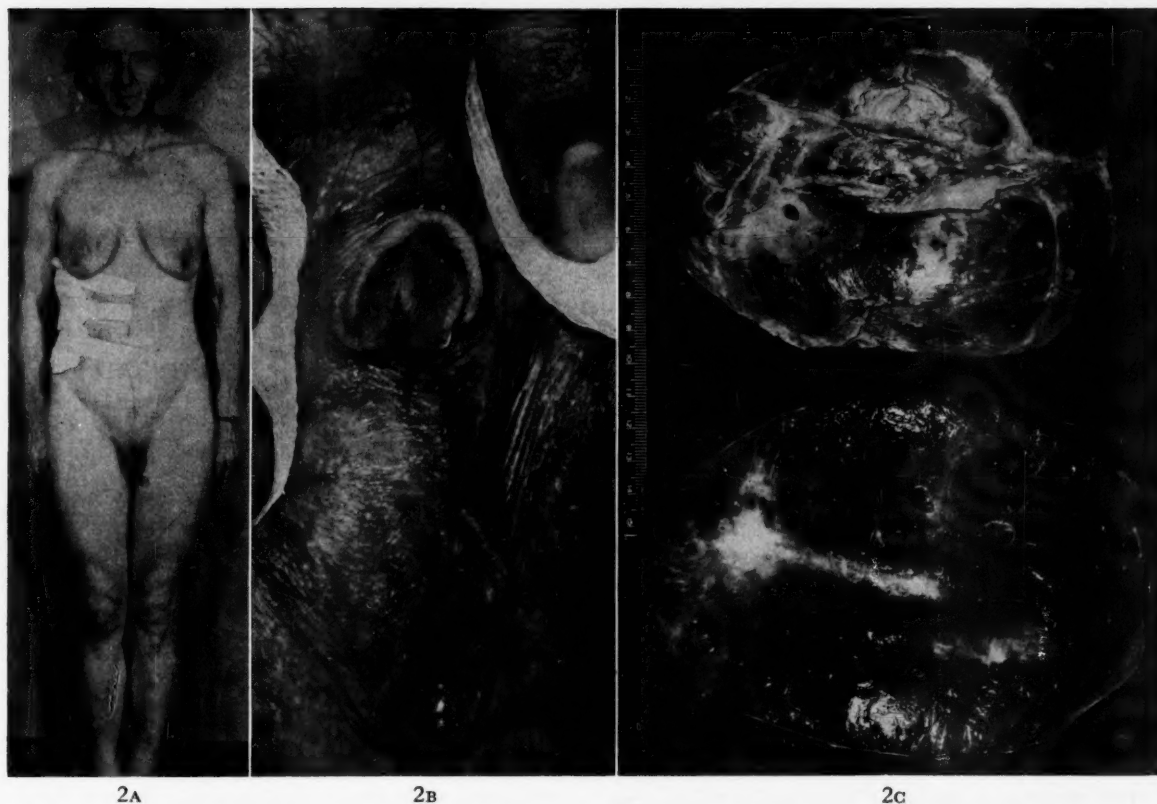


FIG. 2. Adrenogenital syndrome in a lady aged forty-two, having its onset at approximately age twenty. A, masculine configuration; excess hair on face, breasts and abdomen; partial baldness; B, enlarged clitoris; C, adenoma of right adrenal.

steroid excretion is usually normal or slightly elevated and a tumor may be palpated in the ovarian region. The characteristics of benign hirsutism and "mixed syndromes" are discussed later.

Treatment of Congenital Adrenal Hyperplasia. The treatment of the congenital type of adrenogenital syndrome offers problems different from the others because of (1) the embryologic abnormalities in sex differentiation, (2) the very large clitoris and (3) the atrophy of the ovaries. The main decision in therapy is whether to induce the patient to live as a boy or a girl. Although genetically female most of the sex steroids are male and it is usually simpler to have the subject live as a male, especially if the decision is made early in life. Such an individual can be made to appear and function in most respects like a man, ultimately developing a beard, male voice, masculine configuration, excellent strength and a desire to participate in the vigorous activities of a man. Sexual gratification is satisfactory but reproduction is impossible. The chorda, binding the phallus inferiorly, should be cut at an early age; later

plastic operations should be performed to form a penile urethra. If the size of the phallus and other masculine manifestations are not sufficiently prominent, they can be stimulated by the administration of testosterone. Moreover, if the individual is finical, a scrotum can be made from the labia and artificial testes can be implanted.

When the patient has lived for many years as a girl and when the wishes of her and her family are that she continue as such, therapeutic measures should be so directed, especially when the changes are not marked. The major therapy consists of decreasing the hyperadrenocorticism, by means of hormone inhibition or by adrenalectomy, and by performing plastic operations on the clitoris and vulva. Resection of as much as 75 per cent of all adrenal tissue has failed to arrest the progress of the disease. Total adrenalectomy or subtotal adrenalectomy would be expected to be effective, but it has not been established whether this is a satisfactory therapy for the adrenogenital syndrome. When an adrenal tumor is present, it should be removed and therapy for acute adrenal insufficiency be given.

Until recently hormone therapy for the adrenogenital syndrome has not been very effective. In preliminary studies Wilkins¹⁹ found results with cortisone to be encouraging. It caused a decreased excretion of 17-ketosteroids, 11-oxysteroids and estroids.

Since the clitoris is a source of extreme embarrassment, it should be completely or almost completely removed. If the glans is permitted to remain, it may contribute to marked tension; but if it is removed, it may deprive the subject of future sexual gratification. Therefore, opinion varies regarding the choice of procedure. The author chooses to leave the glans because indications are that some of the tension may be controlled with cortisone.

In adolescence plastic operations should be performed to create separate openings for the urethra and vagina. Estrogens are used to develop the breasts and some other secondary sex characteristics. However, some patients are quite resistant to estrogen.¹⁵

Adrenogenital Syndrome in Males

The adrenogenital syndrome in males may be of two general types: (1) hypermasculine and (2) feminine. The former may be due to congenital hyperplasia or to androgenic adrenal tumor; all are quite rare.

Congenital adrenal hyperplasia (macrogenitosomia precox) frequently occurs in siblings but does not occur in successive generations. Often the most prominent manifestations during the first few months of life are those of adrenal insufficiency consisting of vomiting, diarrhea, colic, dehydration and weight loss. Some die without the cause of the disease having been ascertained. The response to adrenal steroid therapy is dramatic.

In some cases the penis is observed at birth to be enlarged, in others the abnormality may not be recognized until the patient is two or three years of age. However, from this age the phallus and prostate enlarge rapidly, reaching adult size at an early age. There is precocious development of sexual hair, some voice changes and libido; erections are frequent. The testes usually are small but occasionally are enlarged; there is no spermatogenesis. General somatic growth is accelerated. The muscles become large and strong. Osseous development is rapid, causing the subject to grow rapidly in height, but the epiphyses close early thereby causing him ultimately to be short.

There is an excessive excretion of 17-ketosteroids; the 11-oxycorticosteroids are in normal or increased amounts. The excessive loss of salt and water account for the clinical manifestations of adrenal insufficiency, but whether the loss is due to a deficiency of a desoxycorticosterone-like substance or excess 17-hydroxycorticosterone⁹ has not been established.

Hyperandrogenism due to congenital hyperplasia of the adrenal may closely simulate that due to tumor but may be differentiated from it by finding the following characteristics of the former: (1) occurrence in siblings, (2) clinical manifestations of adrenal insufficiency and (3) less excess of 17-ketosteroids, especially the beta fraction. However, exploratory laparotomy is sometimes necessary to establish the diagnosis. In precocious puberty of neurogenic origin maturation of the genitalia and spermatogenesis occur at an early age in contrast to the testicular atrophy and aspermatogenesis in macrogenitosomia precox. In the neurogenic type the urinary androgens are in the normal adolescent or adult range. The precocious puberty produced by interstitial tumor of the testis sometimes may be differentiated from congenital adrenal hyperplasia only by testicular biopsy since in each there may also be (1) accelerated body growth, (2) enlarged testis (due to adrenal rests when there is adrenal hyperplasia) and (3) excess androgens in the urine.

The main therapy is that for adrenal insufficiency. Cortisone is of advantage not only in this regard but also in suppressing the hyperandrogenism. When a tumor is present, it must be removed.

Rarely adrenal tumors are encountered in males which cause gynecomastia and impotence. In this group there may be an increase in estrogens and androgens. Therapy consists of removal of the tumor.

Some male adults are observed with possible adrenal hyperandrogenism but it is difficult to establish because of the problem in designating normal limits of masculinity.

CUSHING'S SYNDROME

The term "Cushing's syndrome" is applied differently by authors. Some use it to connote the typical clinical picture associated with basophilic adenoma described by Cushing;²⁰ others call this "Cushing's disease." Some authors apply the term "Cushing's syndrome" to the clinical picture regardless of whether there is a

basophilic adenoma; this connotation is used here. Cushing's syndrome results from hyperadrenocorticism regardless of whether the disease is primary or subsidiary in the adrenals.

Pathology. Whether the primary disturbance in Cushing's syndrome is in the hypothalamus, pituitary or adrenals, or whether it varies in different cases has not been established. Heinbecker²¹ found degenerative lesions in the paraventricular nuclei. Of ninety-eight patients studied by Thompson and Eisenhardt²² sixty were found to have pituitary adenoma, usually basophilic, but rarely eosinophilic or chromophobic. Twenty-two had adrenal tumors; sixteen were malignant and six were benign. Essentially all cases of Cushing's syndrome beginning before ten years are associated with adrenal tumor¹⁵ which often is malignant. When carefully evaluated, one or both adrenals are enlarged in practically all patients. When there is a tumor of the adrenal, whether benign or malignant, there is almost certainty that a basophilic tumor of the pituitary will not be found.⁶ The basophilic adenoma is small, often being located only on microscopic examination; rarely is it large enough to erode the sella turcica.

Crooke²³ changes occur in the pituitary of most patients. These consist of cytoplasmic hyalinization of the basophilic cells, disappearance of the basophilic granules, excessive vacuolization, ballooning of nuclei and general enlargement of the cells. These changes usually are not found in the cells comprising the tumor.

Fibrosis, cysts, infarcts, cancer and fatty necrosis of the pancreas are not uncommon. There also may be hyperplasia of the islets. Atrophy of the striated and smooth muscles, bone and skin is observed. Not uncommonly there are pathologic fractures of the vertebrae. Pyelonephritis, renal calculi, cardiac dilatation and hypertrophy and other changes, described later, are found not infrequently.

Pathologic Physiology. Most of the anatomic and physiologic alterations in Cushing's syndrome are due to hyperadrenocorticism;²⁴ indeed, removal of an adrenal tumor or bilateral subtotal resection of the adrenals has caused disappearance of the clinical syndrome.⁶ As mentioned earlier, it is not known just how many biologically active steroids the adrenals secrete, but there are three general classes of function: (1) impaired glucose utilization and gluconeogenesis, (2) androgenesis and anabolism and

(3) salt and water control. In Cushing's syndrome there tends to be an excess of each of these effects, but the degree of disturbance varies in different patients as does the steroid excretion pattern. There are variations in the amount of obesity, protein depletion, virilization, hypertension, electrolyte balance and carbohydrate metabolism. Most of the classic alterations can be attributed to an excess of the glucosteroids. Indeed, with cortisone therapy in patients without adrenal disease the following changes of Cushing's syndrome have been produced: hirsutism, acne, keratosis pilaris, striae, muscular weakness, mental depression, amenorrhea, edema, hypochloremic hypokaliemic alkalosis, decreased glucose tolerance, insulin resistance and negative nitrogen balance.

The glucosteroids antagonize the synthesis of proteins and since the latter are continually being broken down a general deficiency of protein results. There is an excessive conversion of amino acids to carbohydrate. With the increased manufacture of carbohydrate and its decreased rate of utilization, resulting from the glucosteroid action, there is hyperglycemia. This, with the decreased renal threshold for glucose, produces glycosuria. The excess carbohydrate leads to excess formation of fat; certain adrenal steroids (e.g., 11-dehydrocorticosterone) may accelerate fat deposition, thereby accounting for the obesity in Cushing's syndrome. With tissue protein deficiency the skin and small vessel walls become thin and less elastic. These changes cause the blood vessels to be more prominent, giving a plethoric appearance; they also cause purplish red striae and easy bruisability. There is a general decrease in muscle mass and tone, causing weakness and easy fatigability. The weakness of the muscles of the abdomen wall promotes abdominal protrusion. The protein deficiency along with inhibition of chondrogenesis and osteogenesis retard growth. The decreased protein of the bone is associated with a decreased bone matrix, thereby causing osteoporosis, which when marked is associated with pathologic fractures, especially of the vertebrae; this may produce dorsal kyphosis and pain in the back. The excessive excretion of calcium in the urine causes decalcification of bones, promotes the development of renal calculi and the latter with glycosuria, conduces to the development of pyelonephritis. The decreased body protein and the excess adrenal steroids probably antagonize the secretion of

gonadotropins and thereby cause amenorrhea. The anti-anabolic effects also inhibit growth in children. The eosinopenic, lymphopenic and granulocytotic effects of the glucosteroids account for the respective changes commonly observed in Cushing's syndrome. The effect of these steroids on antigen-antibody reactions and their capacity to inhibit the cytologic responses to injury contribute to the susceptibility of these patients to infections and delay wound healing. The erythrogenic effect of the glucosteroids contributes to the occasional development of mild polycythemia. The increased excretion of the 11-oxycorticoids in the urine results from increased manufacture of glucosteroids. The androgenic steroids and/or glucosteroids apparently account for acne, hirsutism, seborrhea, enlarged clitoris and increased 17-ketosteroid excretion. The androgens promote protein synthesis while the glucosteroids antagonize this. Thus, the clinical picture can be modified considerably by the relative amounts of steroid present. An increased secretion of a desoxycorticosterone-like steroid could explain the development of hypertension, decreased serum potassium and increased serum sodium, but it has not been established whether such a steroid is secreted. As discussed earlier, it is possible that 17-hydroxycorticosterone could be responsible for the three main types of adrenal function, with its effects varying with alterations in its metabolism.

Considerable discussion has been related to whether the primary disturbance in Cushing's syndrome was in the hypothalamus, pituitary or adrenal. Heinbecker²¹ found atrophy of some nuclei in the hypothalamus, particularly the paraventricular. He postulated that these lesions might release an inhibiting effect on the pituitary, leading to excessive secretion of adrenocorticotrophin. Some individuals have reasoned that the primary changes were in the pituitary because a basophilic adenoma and Crooke changes were often present and because there frequently is bilateral hyperplasia of the adrenals. Recently, however, it has been observed²⁶ that patients without adrenal disease treated with ACTH showed an increase in basophils, Crooke's hyaline cytoplasmic changes and basophilic stippling of many of the chromophobes. In patients with Cushing's syndrome and a neoplasm of one adrenal it is often found that the other adrenal is atrophic. This phenomenon could be interpreted as indicating that the

disturbance was primary in one adrenal and that with the excess steroids ACTH release from the pituitary was inhibited, thereby permitting atrophy of the other adrenal.

Clinical Manifestations. Cushing's syndrome is much more common in females. It rarely begins in the first decade, but often starts in the second and third. When it does appear in the first decade, it is almost always associated with an adrenal tumor; subsequently it may be due to bilateral hyperplasia or tumor. In a patient with the classic picture of Cushing's syndrome there are numerous and well defined clinical changes. (Fig. 3.)

1. *Body configuration:* The extremities are relatively small while the trunk is large. The abdomen is quite protuberant (typical "pot-belly"). The face is rounded and sometimes moon-shaped. The neck is short and of increased circumference; a double chin is common. The soft tissues in the suprascapular regions protrude upward and there is a prominent "hump" in the cervicodorsal area giving a "buffalo" appearance. There is dorsal kyphosis and the shoulders are "rounded."

2. *Skin and subcutaneous tissue:* The skin is thin and has a decreased elasticity. Over the arms and legs it not uncommonly is dry and scaly. The hair is usually black or dark and may be increased all over the body; the amount on the face may necessitate daily shaving in females as well as males. There may be acne (Fig. 4) and seborrhea. The face appears plethoric; it often is fiery red but sometimes has a cyanotic hue. The skin over the extremities is often cyanotic and mottled. The veins over the abdomen are readily visible but not engorged. Varicosities in the legs are common. Ecchymoses, especially over the legs, are present. Reddish-purple striae are commonly found over the lower abdomen, thighs, girdle and pectoral regions. They are roughly parallel and depressed and vary from 0.5 to 5 cm. in width and 5 to 15 cm. in length.

There is a relative increase of the fat layer over the abdomen and chest. Palpation of the upper thighs gives a sensation which is difficult to describe but is fairly specific for Cushing's syndrome. The underlying fat lobules are readily felt through the thin and inelastic skin; they are easily moved about as though the interlobular septa were not holding them tightly. The oculi bulbi may protrude and there is an increase in the size of the superior and

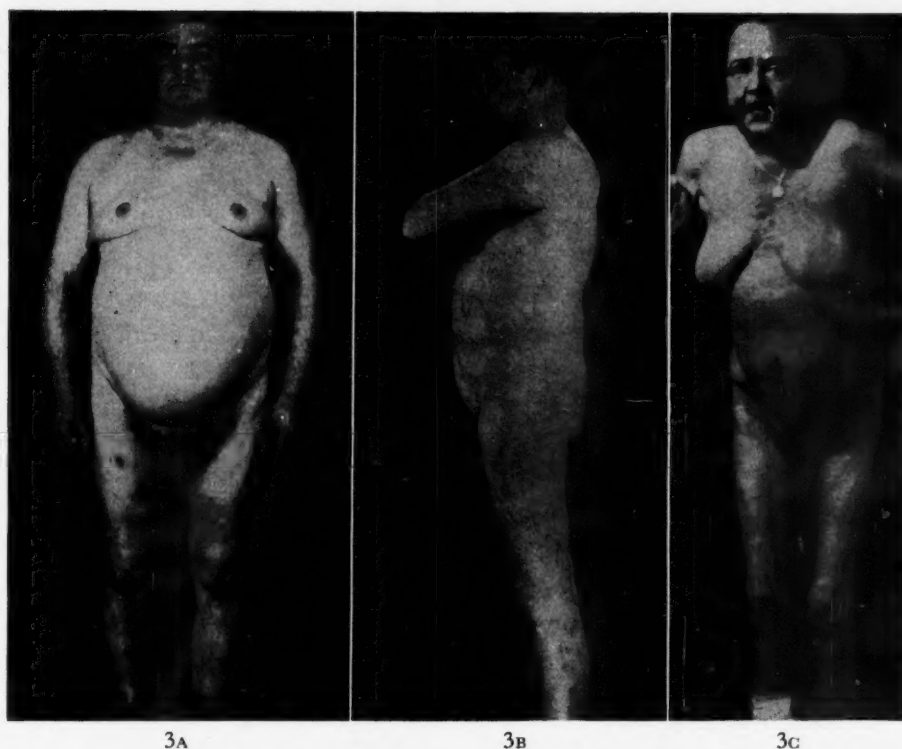


FIG. 3. Cushing's syndrome. A, trunk obesity, moon-shaped face, short, thick neck, supra-scapular padding, plethora, ecchymoses on legs; B, full face, double chin, trunk obesity, striae, ecchymoses; C, another case showing frontal baldness, rounded face, marked atrophy of extremities with weakness so marked to require support; breasts normal.

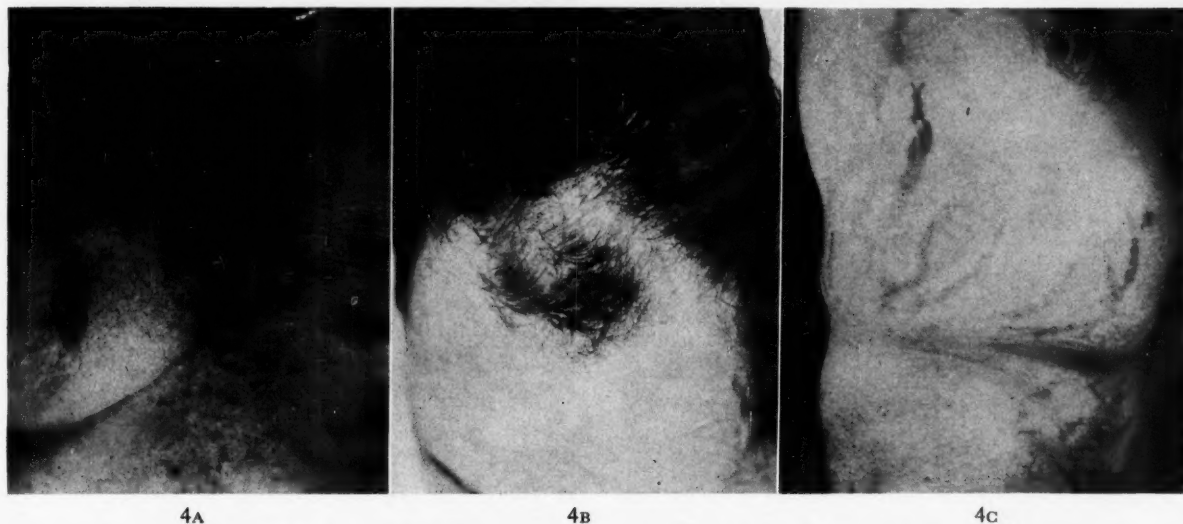


FIG. 4. Cushing's syndrome. A, acne; B, partial baldness in a lady; C, striae; protuberant abdomen.

inferior palpebral fat pads. Sometimes the conjunctivae have a glistening and gelatinous appearance. These changes resemble, to some extent, those found with pituitarigenic ophthalmopathy of Graves' disease.

3. *Muscles*: The muscles are everywhere atrophic and somewhat atonic, but this is more readily apparent in the extremities, especially

in the thighs. (Fig. 3c.) On careful examination it can be observed that much of the abdominal protuberance is due to its thin and atonic muscles. Weakness and easy fatigability are prominent manifestations of the disease; indeed, the patient may become bed-ridden because of weakness.

4. *Skeleton*: Osteoporosis, involving especially

the spine and pelvis, is common; the skull is rarely and the lamina dura is almost never involved. Occasionally there is osteomalacia. The vertebrae are narrow, biconcave and are separated by large biconvex intervertebral discs. Compression fractures in the lower thoracic and upper lumbar vertebrae are common. These cause pain in the back and along the nerve roots. Occasionally there are rib fractures. Very rarely there is erosion of the sella turcica. When the disease appears in children, short stature results and epiphysal development is delayed.

5. *Cardiovascular system:* Hypertension is very common; it may be mild, moderate or severe, but most often it is moderate. There is cardiac hypertrophy and sometimes dilatation along with congestive failure. Rarely there are electrocardiographic indications of hypokaliemia. Arteriosclerosis, especially of the coronaries, occurs with increased frequency. Cerebrovascular accidents are common.

6. *Kidneys and urine:* Pyelonephritis, benign nephrosclerosis and renal calculi occur with increased frequency. There is an increased excretion in the urine of nitrogen, uric acid, sugar, calcium, phosphorus, potassium, chloride and of 11-oxycorticosteroids. The 17-ketosteroids may be present in normal, decreased, slightly increased or markedly increased amounts. Occasionally, the estrogens are excreted in increased quantities. Adrenotropin assays have been unsatisfactory; gonadotropins are not increased.

7. *Sexual changes:* Amenorrhea and loss of libido are common. Enlargement of the clitoris occurs occasionally along with a deep voice. Development of the breasts, vagina and other female characteristics may be inhibited, but occasionally there is precocious development of sexual characteristics in boys and girls. Often there is impotence and some atrophy of the testes.

8. *Blood:* The blood volume is usually normal. Sometimes there is mild polycythemia and erythroid hyperplasia of the marrow. Often there is lymphopenia, eosinopenia and an increase in the neutrophilic granulocytes. Rarely there is hypernatremia, hypokaliemia, hypochloremia and an increase in the bicarbonate. The calcium, phosphorus and phosphatase are usually normal. The cholesterol is sometimes increased and the glutathione decreased. In most instances there is hyperglycemia which is markedly resistant to insulin.

Differential Diagnosis. Cushing's syndrome in its classic form is an easy diagnosis to make; even

the general appearance is almost pathognomonic. Rarely can the diagnosis of a pituitary adenoma be made clinically. The differentiation of the mild and less definite instances from other forms of hyperadrenocorticism and other diseases is discussed in a subsequent section.

In the classic instances of the syndrome the main problem is to determine whether there is an adrenal tumor. This decision often cannot be made with assurance without a surgical exploration. This procedure is more dependable and essentially as safe as perirenal air injection, but is more distressing to the patient, physically and psychologically. Surgery usually excludes all tumors of the adrenal glands that are not aberrant.

Aside from surgical exploration there are a number of considerations that are helpful in establishing reasonable probabilities about the presence of a tumor. As mentioned before, a tumor is essentially always present when the disease begins before the age of ten. Most of the patients who have all of the features of Cushing's syndrome and no significant manifestations of the adrenogenital syndrome have adrenal cortical hyperplasia; patients with prominent manifestations of the adrenogenital syndrome and Cushing's syndrome are more apt to have an adrenal tumor.

Rapid progression of the disease is more likely to be associated with neoplasm. The excretion of more than 50 mg. of 17-ketosteroids per day with a beta fraction exceeding 50 per cent, strongly suggests adrenal tumor⁶ while the excretion of 20 to 50 mg. with a normal beta fraction suggests hyperplasia. However, occasionally there may be considerable deviation; for example, with tumor the beta fraction may be normal and the total excretion may be normal or low.

Treatment. The chief therapy in Cushing's disease consists in removing an adrenal tumor, bilateral subtotal adrenalectomy, irradiation of the pituitary or the use of testosterone to inhibit the release of ACTH and to antagonize glucosteroid action. Hypophysectomy is not recommended.

Albright²⁴ has obtained beneficial results with testosterone. This compound has a potent anabolic effect which antagonizes the anti-anabolic effect of glucosteroids. Moreover, it is thought to decrease the output of these steroids by inhibiting the secretion of ACTH. Testosterone promotes retention of potassium, sulfur,

calcium, phosphorus and nitrogen. It produces an increased rate of synthesis of protein which leads to increased thickness of the skin, muscles and bone matrix. There is a decreased excretion of 11-oxycorticosteroids. With these changes there is decreased bruisability, increased muscle strength and recalcification of bones. Diabetes improves but there is no improvement in the hypertension. Manifestations of hyperandrogenism are intensified by the therapy but this usually is of no consequence even in women. A satisfactory dosage is 25 mg. of testosterone propionate every two days for two months, then 20 to 50 mg. of methyl testosterone daily. Stilbestrol, 5 mg. daily, is sometimes used for a few weeks in conjunction with testosterone because of its capacity to increase bone formation. Irradiation of the pituitary is very effective in some patients but in the majority the response is slow or absent.

Patients with adrenal tumor have the best opportunity for cure provided the tumor has not metastasized and provided adequate therapy is given to prevent adrenal insufficiency. There is almost always significant atrophy of the adrenal not bearing the tumor. While compensatory hypertrophy eventually ensues, severe adrenal insufficiency may occur immediately postoperatively. It is recommended that approximately 100 mg. of ACTH be given for two days preceding the operation and for four days thereafter, with subsequent gradual reduction and elimination of dose. On the day of operation and on two succeeding days 200 mg. of cortisone is administered. Desoxycorticosterone is not given. Adrenal cortical extract is used only in acute emergencies, e.g., hypotension, fever or cyanosis. Plasma, sodium chloride, potassium, glucose and water are given in accordance with the results of careful evaluations of plasma volume, electrolyte concentration, etc.

Experience with bilateral subtotal adrenalectomy has been limited. Kepler reported⁶ the results with nineteen patients. All of one gland and from 70 to 90 per cent of the other were removed. Five patients died within six weeks. Fourteen experienced remissions which were complete in most instances. One patient had a reappearance of the manifestations after a remission that lasted for four years. None developed chronic adrenal insufficiency. The postoperative course was relatively smooth for two or three weeks, but then the patients developed anorexia, vomited and refused to eat. The blood

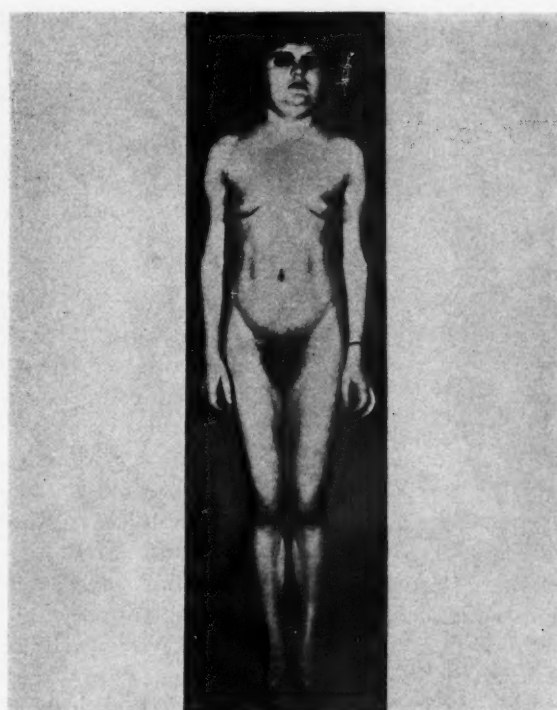


FIG. 5. Female aged eighteen with some manifestations of the adrenogenital and Cushing's syndrome: round face, double chin, short, thick neck, small breasts, male escutcheon; masculine configuration of legs. (From BISSELL, G. W. and WILLIAMS, R. H. *Ann. Int. Med.*, 22: 773, 1945.)

pressure remained at hypertensive levels; the clinical picture was not regarded as one of adrenal insufficiency. Therapy with cortical extract, desoxycorticosterone and saline was ineffective.

Essentially no hormone therapy is required with removal of the first adrenal. Upon removing the second it is recommended that 300 mg. of cortisone be given on the day of and the day following operation, with gradual elimination during the next ten days.

MIXED, PARTIAL AND ALLIED SYNDROMES

The clinical entities discussed thus far have been classic examples of adrenogenital or Cushing's syndrome. However, a greater number of patients exhibit mild or limited characteristics of these syndromes or mixtures of them than the classic picture. There are many combinations of clinical manifestations and several gradations of their severity. Because many of the criteria are not clearly defined, clinicians vary in their classification of these patients.

When there is hypertension, diabetes and striae due to hyperadrenocorticism, there may

be marked hirsutism and slight enlargement of the clitoris, but there is almost always a decrease in muscle mass and strength. When virilism (not just hirsutism) is marked, the manifestations of Cushing's syndrome tend to be absent or insignificant. There are patients like the one in Figure 5, however, who have a masculine configuration, heavy beard, male escutcheon, hypertrophied labia majora and clitoris, infrequent menses, increased 17-ketosteroid excretion, but who also have hypertension, adrenal type of diabetic sugar curve, osteoporosis, round face, buffalo shoulders, increased excretion of 11-oxycorticosteroids and bilateral hyperplasia of the adrenals. Strikingly absent are weakness and the typical skin changes of Cushing's syndrome. The author regards these patients as having "general" hyperadrenocorticism. They are not classic examples of Cushing's syndrome nor of the adrenogenital syndrome but they have definite manifestations of each. The prognosis is much better than that of a patient with typical Cushing's syndrome. The androgens and glucosteroids exert antagonistic effects. Some patients, such as the one shown in Figure 3B, have hypertension, typical striae and other skin changes, trunk obesity, facies of Cushing's syndrome, decreased strength, increased excretion of 17-ketosteroids and 11-oxycorticosteroids, but no abnormality demonstrable by the glucose, insulin or glucose-insulin tolerance tests. The author regards such patients as having Cushing's syndrome although lacking in some of its characteristics. The course is less rapidly progressive than that of patients with the complete picture.

Not uncommonly there are patients who have many of the clinical disturbances that patients with Cushing's syndrome have, but the author prefers not to designate them as Cushing's syndrome, even though there is a probability that they have hyperadrenocorticism; this is because there are many qualitative and quantitative clinical differences and a much better course. These patients may have hypertension, diabetes, obesity, round face, double chin, short and thick neck, cervical-thoracic "hump," dorsal kyphosis, hirsutism, questionably enlarged clitoris, enlarged labia majora, amenorrhea and decreased libido. However, upon carefully analyzing the individual components of the picture and their course of development, it is evident that there is a considerable difference in these patients from those who have typical

Cushing's syndrome or adrenogenital syndrome. The obesity is generalized. The skin is thick, taut and quite elastic. The blood vessels are not prominent. There are no red striae and no ecchymoses. The strength is essentially normal, occasionally better than normal. There is no muscle atrophy, no osteoporosis and no hemocytologic changes. The 17-ketosteroid and 11-oxycorticosteroid excretion is usually normal; occasionally it is slightly elevated; the 17-ketosteroids are sometimes subnormal. The diabetes* is predominantly of the hypoinsulin type. The author has suspected that such a picture might be at least partially due to hyperadrenocorticism but with a difference in the relative quantities of steroids found in Cushing's syndrome; e.g., could an increase in 11-dehydrocorticosterone be an important factor? There is no proof of such; indeed Kendall¹⁴ doubts that the adrenal secretes 11-dehydrocorticosterone. The prognosis of these patients is governed chiefly by the hypertension, diabetes and obesity.

The disturbances described in the preceding paragraph are found in varying combinations and most often without the complete list of disorders. Some of these patients who have frontal hyperostoses are said to have the syndrome of Morgagni, but it is my impression that the hyperostoses are coincidental.

Special consideration is deserved for patients who have hirsutism, who may or may not have other disturbances, but who do not have Cushing's syndrome or well defined adrenogenital syndrome. The general health of these patients is excellent. As stated by Bissell²⁶ "the bearded lady is to the public amusing, to the showman profitable, to the physician physiologically fascinating—and to herself, utterly miserable." Psychoneurosis is common; suicide is often considered and occasionally committed.

It is the author's impression based upon studies of this problem (reported²⁶ in part) over a period of several years that most of these patients have as the etiology of their hirsutism one of three causes: (1) hyperadrenocorticism, (2) hypersensitivity of the hair follicles or (3) factors (1) and (2). Hirsutism is more common in certain races than others. It is especially prone to occur in Italians and Jews. Sometimes every member of a large family may have it. On the other hand,

* In many markedly obese patients without diabetes, even in those with "simple obesity" there is resistance to insulin as indicated by the glucose-insulin tolerance test.²⁶

Indians tend to have little hair anywhere except on the scalp. Danforth²⁴ states that although a humoral control of human hair follicles exists, the final product of each individual follicle is largely determined by constitutional factors within the hair cell itself. That hair follicles have different thresholds of response in a normal individual is indicated by the fact that two hairs may be of the same appearance until puberty when one (e.g., in the axilla) may become long and coarse whereas the other (e.g., on the back) may remain unchanged.

However, there are clinical factors that occur in conjunction with the hirsutism to suggest that in some of these patients there is hyperadrenocorticism. Yet the quantity of 17-ketosteroids in the urine is usually normal or at the upper limit of normal; occasionally it is slightly increased or subnormal. In interpreting 17-ketosteroid values it is important to realize that in this determination (1) one is measuring a mixture of steroids, (2) the procedure is not entirely accurate technically, (3) some 17-ketosteroids are not androgens, (4) one of the most potent androgens (testosterone) is not a 17-ketosteroid and only part of it is excreted as a 17-ketosteroid and (5) an androgen (methyltestosterone) may actually depress the 17-ketosteroid secretion. One must also bear in mind that there is evidence to indicate that much larger quantities of androgens are needed to produce hirsutism than to maintain it; there is a possibility that at puberty or some other time there is transiently a marked excess in the secretion of androgens and later a decrease to such levels that are not of sufficient excess to be demonstrable by our assay technics. It must also be borne in mind that because of the many factors causing adrenomegaly it is difficult to be sure at necropsy²⁸ just what is the main factor responsible. The situation is simpler with respect to adrenals removed surgically.

In most instances the hirsutism begins between the ages of fourteen and twenty-four. The ultimate amount of hair varies from a slight excess on the face, suprapubic region or extremities to a heavy coat of coarse black hair over the entire body, frequently causing the patient to shave the face and extremities. The skin is thick, oily and sometimes has acneiform lesions. There is usually more than average strength and muscle mass. The voice may or may not be slightly low-pitched. The breasts may be normal or small; rarely are they large. (Fig. 6.) The clitoris is usually stated to be of normal size.



FIG. 6. Hirsutism without definite virilism. Note facial hirsutism; breasts are large. (From BISSELL, G. W. and WILLIAMS, R. H. *Ann. Int. Med.*, 22: 773, 1945.)

However, there are no good criteria for determining the upper limit of normal; it is the author's impression that the average size of the clitoris of these subjects is definitely greater than the average for the non-hirsute and that some of them can be stated to be enlarged. Menses may be normal in all respects but they tend to be infrequent and irregular. There is a tendency for slight to moderate obesity. Most of these patients do not have hypertension or diabetes.

Unfortunately, treatment of this group of patients is one of the most distressing problems which confronts the endocrinologist. Removal of hair from exposed parts of the body and psychotherapy are essentially all that he has had to offer. Endocrine therapy has not proved satisfactory thus far.

SUMMARY

The most classic manifestations of hyperadrenocorticism are found in Cushing's syndrome and the adrenogenital syndrome. Dramatic results can be obtained in the treatment of these patients when the main pathogenetic factor is

an adrenal tumor, which is satisfactorily removed in its entirety. In Cushing's syndrome due to adrenal hyperplasia excellent results have been obtained in some patients following bilateral subtotal adrenalectomy. The prospects of surgical therapy for hyperadrenocorticism loom much brighter with the provision of an abundant supply of cortisone for the treatment of acute and chronic adrenal insufficiency that may be complications of surgery. Testosterone therapy is of some advantage in the treatment of Cushing's syndrome and cortisone in the adrenogenital syndrome.

Far more common than either of these syndromes is a miscellaneous group of patients with certain manifestations, but with a course that is quite different. The pathogenesis, pathologic physiology and rationale of therapy for this larger group of patients is much less clearly understood.

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Adrenal Medullary Function*

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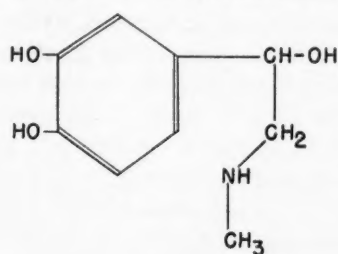
I. HORMONES OF THE ADRENAL MEDULLA

Chemistry

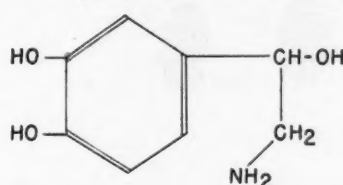
Separation of Nor-epinephrine from Epinephrine. Epinephrine was the first hormone to be isolated and chemically identified. Its synthesis in 1904

ologically active one, the dextro-compound showing only 3 to 4 per cent of the levo activity.⁷

Adrenal medullary and other chromaffin tissue show close embryologic and functional relationship to the sympathetic nervous system. If two sympathetic mediators exist, nor-epi-



EPINEPHRINE



NOR-EPINEPHRINE

FIG. 1.

ended, for practical purposes, biochemical research on the adrenal medulla. It was only during the last few years that the pharmacologic discovery of the primary amine nor-epinephrine in adrenergic nerve fibers led to a re-investigation of the chemistry of the medullary hormone.

Nor-epinephrine (arterenol; nor-adrenaline) is a primary amine differing from epinephrine only by the absence of an N-methyl group. (Fig. 1.) Its presence in the mammalian body was first demonstrated by von Euler by pharmacologic methods; extracts of postganglionic adrenergic nerves of cattle (splenic nerves) showed an activity corresponding to 10–15 μ g. of l-nor-epinephrine per gm. of tissue.^{1,2} Its functional importance as sympathin E had previously been suggested by Bacq³ and as a possible precursor of epinephrine by Blaschko.⁴ The final proof of a release *in vivo* of nor-epinephrine on excitation of adrenergic nerves was produced by Peart working in Gaddum's Institute.⁵ The separation of levo nor-epinephrine from a racemic mixture by Tullar⁶ made it possible to demonstrate that as in the case of epinephrine the levo compound was the physi-

nephine and epinephrine, one would expect the adrenal medullary hormone also to be of dual nature. This was first suggested by Holtz and Schümann in 1948⁸ who found that the rise of blood sugar produced by an extract of the adrenal medulla of cattle corresponded to that of a mixture of 75 per cent epinephrine and 25 per cent nor-epinephrine rather than to that of pure epinephrine. Definite chemical proof was given in 1949 by Goldenberg et al.,⁹ Tullar¹⁰ and Bergstrom et al.¹¹ Extracts of the adrenal medulla of cattle (epinephrine U.S.P.) were shown to contain about 18 per cent nor-epinephrine by chromatographic analysis on paper. (Fig. 2.) A modification of James'¹² method was used for the separation of nor-epinephrine from epinephrine (solvent: phenol, water and 8-hydroxyquinoline). These findings were communicated to Dr. Tainter in 1948 and led to the isolation of l-nor-epinephrine as bitartrate from "natural" epinephrine U.S.P. by Tullar.¹⁰ Further confirmation was given by Bergstrom, Euler and Hamberg¹¹ who succeeded in isolating nor-epinephrine from adrenal extracts by countercurrent distribution. A previously at-

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tempted chromatographic separation using butanol-HCl as solvent¹³ could not be confirmed.^{14,15}

The nor-epinephrine content of the adrenal medulla varies from species to species. Rabbit's adrenals contain little if any nor-epinephrine. In contrast cat's adrenals contain about 50 per

the vascular architecture of the adrenal gland is such as to provide an ample supply of ascorbic acid to the central (medullary) part of the gland. So far the only established function of ascorbic acid in the adrenal gland is its anti-oxidant action protecting the secreted adrenaline.¹⁹

Quantitative Determination. Three chemical methods for the estimation of epinephrine and nor-epinephrine have proved of value:

Paper partition chromatography using James' modified method^{9,12} permits also quantitative determination by planimetry of the epinephrine and nor-epinephrine spots. The quantitative estimation on paper is tedious and is used by us only when the colorimetric method quoted below cannot be applied, as for the determination of small epinephrine fractions in tumors containing more than 95 per cent nor-epinephrine.²⁰

von Euler and Hamberg's²¹ colorimetric method is based on the fact that epinephrine can be easily oxidized by 0.1 normal iodine at pH 4, with the formation of iodoadrenochrome, whereas at this pH only about 10 per cent nor-epinephrine is oxidized. At pH 6 both epinephrine and nor-epinephrine are fully oxidized.

The chromatographic method permits determinations of epinephrine or nor-epinephrine to a lower limit of 2 micrograms. The colorimetric method shows a lower limit of about 10 micrograms of either compound. This makes both methods unsuitable for the determination of epinephrine and nor-epinephrine in plasma or in urine extracts except in special cases as urine extracts of pheochromocytoma in which chromatography appears feasible.

The fluorimetric method as recently developed by Lund promises to cover a range down to 10 m μ g./ml. of epinephrine.^{22,23} This method constitutes the first attempt of a "specific" fluorimetric determination of epinephrine (and norepinephrine?). It is based on the oxidation of epinephrine to adrenochrome by the use of manganese dioxide and rearrangement of the adrenochrome so produced into the fluorescent adrenolutine by use of sodium hydroxide-ascorbic acid. (Fig. 3.)

In contrast to previous fluorimetric methods the determination is not performed directly on plasma but is preceded by adsorption. Plasma diluted with a sodium acetate solution is filtered through a column of aluminum oxide. After washing the column the adsorbed epinephrine is eluted with acetic acid. By the use of this adsorption procedure the method achieves

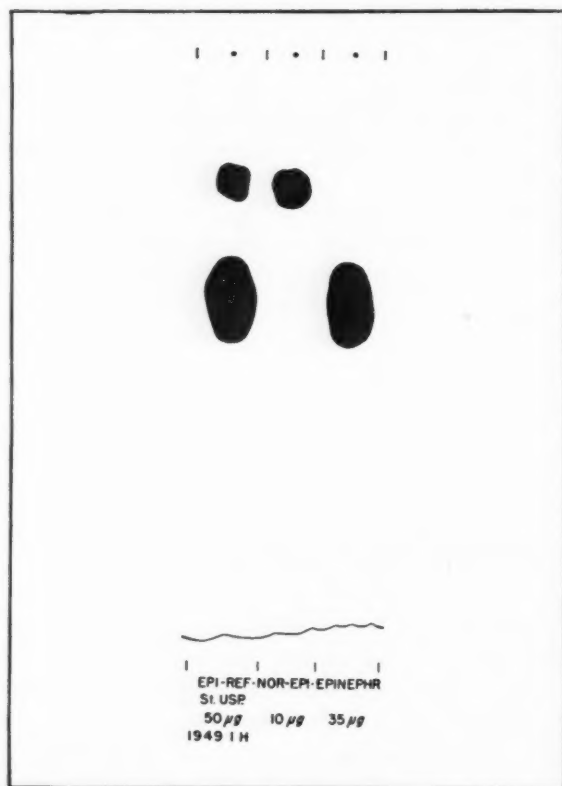


FIG. 2. Paper chromatogram showing (on left) the presence of both epinephrine and nor-epinephrine in extracts of cattle adrenals (epinephrine U.S.P.).

cent nor-epinephrine in the catecholamine fraction. Cattle adrenals contain about 20 per cent and so do human adrenals (10 to 30 per cent).¹⁶⁻¹⁸

Using phenol-water-8-hydroxyquinoline as solvent and ferricyanide as indicator, chromatographic analysis of adrenal extracts of various animal species showed regularly a third lilac colored spot with an R_f intermediate between nor-epinephrine and epinephrine.¹⁸ This spot corresponds to ascorbic acid. The highest content was found in animal species whose adrenals contain hardly any nor-epinephrine, as rabbit's adrenals. A similar relation seems to exist in pheochromocytomas, the highest ascorbic acid values being found in tumors containing epinephrine predominantly. Analytic data show that by far the largest portion of the ascorbic acid is present in the adrenal cortex. However,

specificity. The determination of nor-epinephrine as suggested by Lund is based on differential oxidation at pH 3 and 6 similar to von Euler's colorimetric method.²⁴

Biosynthesis. Little is known about the formation of epinephrine and nor-epinephrine *in vivo*.

true for the oxidation rate of nor-epinephrine has not been established to our knowledge.

Richter suggested that the main pathway of inactivation may be esterification (probably with sulfuric acid) followed by excretion in the urine.³³ Normal urines contain a mixture of

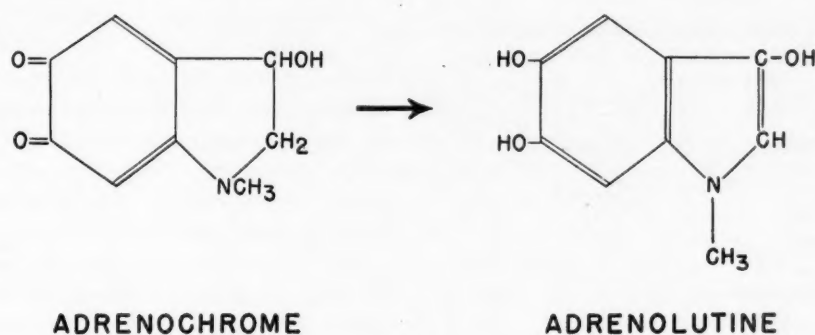


FIG. 3.

Phenylalanine has been regarded as precursor.²⁵ The following steps, involving the transformation to 3,4-dihydroxyphenylalanine and then decarboxylation to hydroxytyramine, are merely hypothetical, but suggested by the presence of enzyme systems capable of catalyzing these reactions in the mammalian body. Tyrosinase has been found in skin²⁶ while dopadecarboxylase is present in kidney, liver^{27,28} and the adrenal medulla.²⁹ Nothing is known about the final introduction of the hydroxy group into the side chain. Another pathway has been suggested by the recent findings that dihydroxyphenylserine can be decarboxylated by mammalian tissue.³⁰ Methylation of nor-epinephrine by minced adrenal medulla with choline as donor has been claimed by Bulbring.³¹

Inactivation. The observation that epinephrine and to a somewhat lesser degree nor-epinephrine at pH 7 are easily oxidized when exposed to air with the formation of adrenochrome and nor-adrenochrome poses the question whether a similar inactivation mechanism occurs in mammalian tissues. Bacq³² advocates this mechanism suggesting that cytochrome-indophenoloxidase may represent the required enzyme system, but proof is lacking. Adrenochrome was found in a chromaffin tissue tumor²⁰ which was worked up immediately after operative removal of the tumor so that the presence of adrenochrome as an artefact can probably be excluded.

The action of amine-oxidase³³ appears to be too slow to explain the rapid inactivation of epinephrine in the body. Whether this is also

approximately 85 per cent nor-epinephrine and 15 per cent epinephrine partly esterified, the twenty-four-hour excretion amounting to about 15 to 45 micrograms nor-epinephrine equivalent.^{17,34,35} The principal source of these catecholamines is not the adrenal medulla since cases of Addison's disease with complete destruction of both adrenals by tuberculosis may show high normal or even above normal values.³⁵ The fraction recovered in urines following infusion of nor-epinephrine amounts to less than 2 per cent and makes it questionable whether this is an important pathway of inactivation.³⁶

Pharmacology

A discussion of the pharmacology of epinephrine will be omitted since textbooks may be consulted for details. In discussing the pharmacology of nor-epinephrine its actions in man will be considered primarily because species differences make deductions drawn from animal experiments not *a priori* applicable to man. How much the action of nor-epinephrine in its relation to epinephrine differs from species to species and from tissue to tissue is apparent from West's table.³⁷ (Table 1.)

Nor-epinephrine was first pharmacologically investigated by Barger and Dale³⁸ and found to show much weaker inhibitory effects on smooth muscle than epinephrine and to mimic some of the effects of sympathetic nerve stimulation better than epinephrine.

Hemodynamic Effects of Epinephrine and Nor-Epinephrine. The classic pharmacologic con-

ception of the pressor action of epinephrine is that it depends chiefly on intense vasoconstriction, the direct cardiac action being only accessory. The hypotensive action of epinephrine in small doses (cat) reported as early as 1900 and extensively studied by Cannon and Lyman³⁹

TABLE I*

EFFECT OF RATIO OF DOSE OF L-NOR-EPINEPHRINE TO EQUI-ACTIVE DOSE OF L-EPINEPHRINE ON VARIOUS FRESH PREPARATIONS

Test Object	Ratio	Exciter (E) or Inhibitor (I) Action
Cat—Blood pressure	0.4	E
Cat—Pregnant uterus	0.4	E
Cat—Ileum	0.5	I
Cat—Nictitating membrane	0.6	E
Rabbit—Ileum	1.0	I
Rat—Ileum	1.5	I
Rabbit—Pregnant uterus	2.0	E
Rabbit—Non-pregnant uterus	2.5	E
Frog—Blood vessels	2.5	E
Frog—Straub heart	4.0	E
Cat—Non-pregnant uterus	5.0	I
Frog—Perfused heart	16.5	E
Rat—Non-pregnant uterus	50.0	I

* From WEST, G. B. *J. Physiol.*, 106: 418, 1947.

has been generally regarded as of minor physiologic importance. Starr and his co-workers⁴⁰ and Ranges and Bradley,⁴¹ using ballistocardiographic output determination, found that subcutaneous administration of therapeutic amounts of epinephrine in man resulted in increased cardiac output, decreased peripheral resistance

which was used in these investigations prevented general acceptance of these results.

By using a more rigorous method of cardiac output determination (right heart catheterization: Fick principle) and extending the investigation to nor-epinephrine, the hemodynamic pattern of epinephrine in man was fully clarified.⁴²

The amines were administered by continuous intravenous infusion. The infusion of nor-epinephrine was followed by prompt increase in both systolic and diastolic blood pressures due to an impressive augmentation of total peripheral resistance. Cardiac output was little affected, if anything, decreased, and the subjects were so strikingly free of symptoms as to be frequently unaware that any change had occurred in their vascular dynamics. The hypertensive effect of equal amounts of epinephrine, on the other hand, was due primarily to a large increase in the cardiac output which overbalanced the constantly observed decrease in total peripheral resistance. Epinephrine infusion was usually accompanied by tachycardia, palpitation and other symptoms.

Upon intravenous infusion of epinephrine in doses of 0.1 to 0.3 $\mu\text{g./kg./min.}$ for a period of eleven to thirty-seven minutes and of nor-epinephrine in doses ranging from 0.1 to 0.4 $\mu\text{g./kg./min.}$ for a period of eleven to twenty-two minutes hemodynamic changes were observed as listed in Table II.⁴³ Details of two representative experiments are apparent from Tables III and IV.⁴²

TABLE II

CHANGES OF CERTAIN CARDIOVASCULAR FUNCTIONS DURING THE INFUSION OF EPINEPHRINE AND NOR-EPINEPHRINE*

Substance	Cardiac Output	Systemic Blood Pressure			Total Peripheral Resistance	Pulse Rate	Mean Pulmonary Pressure
		Systolic	Diastolic	Mean			
Epinephrine	+++	+++	⊕	+	—	+	++
Nor-epinephrine	÷	+++	++	++	+++	—	++

* From GOLDENBERG et al., *J. A. M. A.*, 140: 776, 1949.

⊕ is no change or slight increase; ÷ is no change or slight decrease.

and diastolic pressure with only a small elevation of systolic pressure. Starr attributed the observed drop of total peripheral resistance which seemed to contradict common pharmacologic experiences to the subcutaneous route of administration with resulting slow resorption of minute amounts of the drug. The criticisms raised against the ballistocardiographic method

Epinephrine and nor-epinephrine resemble one another superficially by producing an increase in systolic and mean arterial pressures. Nor-epinephrine hypertension is due to an increase of total peripheral resistance with no significant change or even a fall in cardiac output, whereas epinephrine hypertension is the result of a significant increase of cardiac output

in spite of a decrease of total peripheral resistance. These findings were corroborated by investigations of blood flow in different vascular beds of the human body.⁴⁴⁻⁴⁸

Muscle blood flow is increased by epinephrine and this is true for intravenous as well as intra-

croft and Konzett⁴⁴ found no change of flow with the increase of pressure seemingly balancing the vasoconstrictor effect. A determination of splanchnic blood flow measured by hepatic clearance⁴⁷ showed an increase of splanchnic blood flow following epinephrine, and no

TABLE III*

HEMODYNAMIC CHANGES OBSERVED DURING THE SUCCESSIVE INFUSION OF EPINEPHRINE
AND NOR-EPINEPHRINE

Case 3, E. G., Normal Male, 30 Years, b.s. 1.74 m²

Time in minutes	0	12	31	55	71
State and drug	Rest	Rest	<i>Epinephrine</i>	Rest	<i>Nor-epinephrine</i>
Dose of drug $\mu\text{g.}/\text{kg.}/\text{min.}$	0.25	0.25
Pulse rate/min.	78	72	72	68	50
Ventilation L./min./m ²	4.2	4.7	6.2	3.9	3.9
Oxygen consumption cc./min./m ²	138	166	206	140	140
Oxygen arteriovenous difference cc./L.	34	35	23	33	43
Cardiac output L./min.	7.04	8.23	15.56	7.39	5.68
Systemic blood pressure mm. Hg					
Systolic	124	120	180	122	184
Diastolic	78	75	87	81	106
Mean	98	94	118	101	138
Total peripheral resistance dynes cm ⁻⁵ sec.	1102	909	601	1090	1915
Mean pulmonary arterial pressure mm. Hg	16	16	25	16	22

* From GOLDENBERG et al., *Am. J. Med.*, 5: 792, 1948.

TABLE IV*

HEMODYNAMIC CHANGES OBSERVED DURING THE SUCCESSIVE INFUSION OF EPINEPHRINE,
NOR-EPINEPHRINE AND A COMBINATION OF THE TWO SUBSTANCES

Case 1, J. S., Normal Male, 26 years, b.s. 1.81 m²

Time in minutes	0	14	34	55	76	93
State and drug	Rest	Rest	<i>Epinephrine</i>	Rest	<i>Nor-epinephrine</i>	<i>Epinephrine and Nor-epinephrine</i>
Dose of drug $\mu\text{g.}/\text{kg.}/\text{min.}$	0.15	0.15	0.15 + 0.15
Pulse rate/min.	64	60	78	60	48	58
Ventilation L./min./m ²	2.9	3.1	4.1	2.7	3.0	3.6
Oxygen consumption cc./min./m ²	144	145	176	142	143	168
Oxygen arteriovenous difference cc./L.	35	39	24	41	50	33
Cardiac output L./min.	7.46	6.72	13.30	6.24	5.18	9.22
Systemic blood pressure mm. Hg						
Systolic	120	121	147	133	162	174
Diastolic	68	70	72	76	91	83
Mean	86	88	96	94	115	111
Total peripheral resistance dynes cm ⁻⁵ sec.	922	1030	577	1205	1785	960
Mean pulmonary arterial pressure mm. Hg	14	14	22	14	19	25

* From GOLDENBERG et al., *Am. J. Med.*, 5: 792, 1948.

arterial administration. Upon intra-arterial administration of nor-epinephrine in comparable doses (3 $\mu\text{g.}/\text{min.}$) a striking decrease of flow occurs. Upon intravenous administration, Bar-

croft and Konzett⁴⁴ found no change of flow with the increase of pressure seemingly balancing the vasoconstrictor effect. (Table v.)

Renal blood flow as determined by diodrast clearance is decreased by both epinephrine and

nor-epinephrine (20–30 $\mu\text{g./min.}$). A quantitative comparison of the action of both amines unfortunately is not available.

The decrease of skin flow with epinephrine is readily observed. With nor-epinephrine different responses depending on the method and

tion has been well known and is apparent from the figures of the experiments quoted previously. (Tables III and IV.⁴²) This action is less pronounced with nor-epinephrine and most likely lacking in a physiologic range. In our nor-epinephrine infusion experiments, doses up to

TABLE V
BLOOD FLOW CHANGES IN DIFFERENT VASCULAR AREAS DURING EPINEPHRINE
AND NOR-EPINEPHRINE INFUSIONS

Area	Epinephrine	Nor-epinephrine	Dosage	Route of Administration	Author
Muscle blood flow	++	0	20 $\mu\text{g./min.}$	Intravenous	Barcroft & Konzett ⁴⁴ Allen et al.
Muscle blood flow	—	10–30 $\mu\text{g./min.}$	Intravenous	Barnett et al. ⁴⁸
Muscle blood flow	++	—	3 $\mu\text{g./min.}$	Intra-arterial	Barcroft & Konzett ⁴⁴
Splanchnic blood flow	+	0	0.1 $\mu\text{g./kg./min.}$	Intravenous	Bearn et al. ⁴⁷
Renal blood flow	—	—	20–30 $\mu\text{g./min.}$	Intravenous	Barnett et al. ⁴⁸
Skin blood flow	—	±	7–20 $\mu\text{g./min.}$	Intravenous	Kappert et al. ⁴⁶
Skin blood flow	—	10–30 $\mu\text{g./min.}$	Intravenous	Barnett et al. ⁴⁸

dosage used were reported. Barnett et al. found a consistent drop of skin flow (10–30 $\mu\text{g./min.}$). Kappert et al.⁴⁶ found a decrease of flow in some experiments but an increase in others (7–20 $\mu\text{g./min.}$).

The algebraic sum of these blood flow changes is quite compatible with the total peripheral resistance changes observed in our experiments. (Table II.)

In the studies on the action of epinephrine cited above it was demonstrated in man that doses of epinephrine up to 0.3 $\mu\text{g./kg./min.}$ produced a systolic hypertension which was due to an increase in cardiac output rather than to an augmentation of peripheral resistance. Our observations in cases of pheochromocytoma suggest that with *larger* doses epinephrine also causes over-all vasoconstriction in man. This view is supported by experiments performed on a case of pheochromocytoma (Case 5, A.C.) before and four months after the tumor was removed.²⁰

Within the range investigated, the intense vasoconstriction caused by nor-epinephrine can be blocked by simultaneous administration of equimolar doses of epinephrine. (Table IV.⁴²) A detailed investigation of this phenomenon, which was attributed to competitive inhibition,⁴² was undertaken by de Largy et al.⁴⁹

Effects on Metabolism. The increase of oxygen consumption following epinephrine administra-

tion has been well known and is apparent from the figures of the experiments quoted previously. (Tables III and IV.⁴²) This action is less pronounced with nor-epinephrine and most likely lacking in a physiologic range. In our nor-epinephrine infusion experiments, doses up to

0.15 $\mu\text{g./kg./min.}$ and, in single experiments, even up to 0.25 $\mu\text{g./kg./min.}$ caused no increase in oxygen consumption.⁴²

Similarly the hyperglycemic effect of nor-epinephrine is weaker than that of epinephrine, an equal response ratio of 1:4–1:8 having been observed.^{20,50}

Effects on Adrenal Cortex. Epinephrine is capable of increasing adrenal cortical secretion.^{51,52} It seems that without exception ACTH is the intermediary of epinephrine activity.^{53,54} The site of action of epinephrine is either the anterior lobe of the pituitary or the hypothalamus.^{55,56} Here again as with other metabolic actions, nor-epinephrine seems to be inert in a physiologic range and the ratio between epinephrine and nor-epinephrine given for the release of ACTH and 11-oxysteroids is similar to the one encountered for the hyperglycemic and calorogenic response.^{57,58}

Effects on Central Nervous System. Epinephrine (as observed in our infusion experiments) appeared to cause restlessness, apprehension and a feeling of anxiety. This central nervous system response was not observed with nor-epinephrine. For a diagrammatic summary of the pharmacologic actions of epinephrine and nor-epinephrine see Figure 4.

Quantitative Estimation of Epinephrine and Nor-epinephrine by Bioassay. The quantitative estimation of epinephrine and nor-epinephrine by

bioassay in plasma and urinary extracts will be discussed under: Pheochromocytoma—pharmacologic diagnostic methods.

II. FUNCTION OF THE ADRENAL MEDULLA

The adrenal medulla is not necessary for the maintenance of life. The consistent proof that

it serves effectively in emergencies; furthermore, that this service can be given a general expression in stating that the system guards the constancy of the internal environment of the organism; and finally that secreted adrenaline itself acts to prolong the effects of nerve impulses, to accelerate metabolism, to shorten coagulation

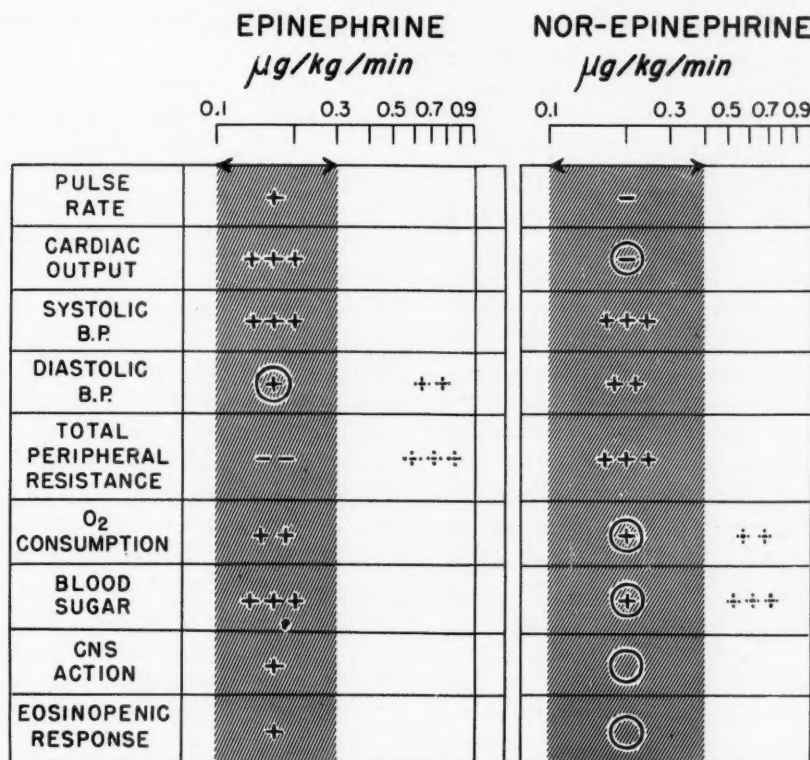


FIG. 4. Comparison of effects of a continuous intravenous infusion of epinephrine and nor-epinephrine. Shaded areas indicate data from studies by Goldenberg and others,⁴² Goldenberg and Aranow,²⁰ Cori and Buchwald⁶⁶ and Madison.⁵⁸ Data reported in light areas are derived from observations on patients with pheochromocytoma.²⁰ Plus signs indicate degree of response; circles indicate response was insignificant; light plus signs indicate preoperative findings. (From GOLDENBERG et al., *Arch. Int. Med.*, 86: 823, 1950.)

the resting secretion of the adrenal medulla lies far below the threshold value for the hyperglycemic and the hypertensive effect of epinephrine led to a proper understanding of its function. It seems appropriate to use Cannon's own words⁵⁹ in defining this "emergency theory": "In summarizing the part played by the adrenal medulla in the functioning of the organism we may recognize that it cooperates with sympathetic impulses in producing adrenaline, that this sympathico-adrenal system is brought prominently and usefully into action in emotional excitement, in vigorous muscular work, in asphyxia, low blood-pressure, chilling surroundings, and hypoglycemia—in brief, that

time and to release glucose from the liver. There is no evidence that secreted adrenaline is an important agent in maintaining high blood pressure."

What are the significant changes in our concept which have developed since? (1) The adrenal medulla produces two hormones, epinephrine and nor-epinephrine and not one as generally accepted until 1949. (2) The sympathetic transmitter is nor-epinephrine or a mixture containing predominantly nor-epinephrine rather than epinephrine. (3) The function of the adrenal medulla in man cannot be defined as an accentuation of sympathetic innervation. On the contrary, in some respects its action is

antagonistic to sympathetic innervation: difference of hemodynamic response to epinephrine and nor-epinephrine in man. (4) Aside from its immediate action as apparent in cardiovascular and the longer-lasting metabolic responses (hyperglycemic effect and increase of oxygen consumption), a delayed action on 11-oxy-steroid output exists which is mediated by an increase in ACTH secretion. Whether other "chain reactions" may be caused by epinephrine and/or nor-epinephrine is not definitely known but is suggested by findings in pheochromocytoma: "secondary hypertension."²⁰ (5) Tumors producing epinephrine and nor-epinephrine (pheochromocytomas) may cause intermittent as well as persistent hypertension.

With the realization that two hormones are present in the adrenal medulla, the question arises whether they are being released independently or are secreted as a mixture of constant proportions. The claim⁶⁰ that an independent secretion of nor-epinephrine from the adrenal medulla occurs on stimulation of the carotid sinus has been definitely disproved,⁶¹ and even a shift of percentage with a prevalence of the non-methylated congener claimed after prolonged splanchnic stimulation⁶² has not been confirmed.⁶³ If one assumes that natural epinephrine as secreted by the adrenal gland constantly maintains a content of let us say 18 per cent nor-epinephrine, our present concepts of adrenal secretion are fully valid since small constant quantities of nor-epinephrine would not significantly alter the functions of epinephrine.⁹ This statement applies to animal species whose adrenal medullary secretion contains a small percentage of nor-epinephrine, e.g., man.

Since nor-epinephrine or mixtures containing predominantly nor-epinephrine serve principally⁵ as sympathetic transmitter, the following functional pattern emerges: Under resting conditions, the vasomotor tone is maintained by the local neuro-humoral secretion of nor-epinephrine. Escaping nor-epinephrine is below the metabolic threshold. Under "emergency" conditions a discharge of adrenal medullary hormone occurs. Since small (10 to 30 per cent) quantities of nor-epinephrine do not significantly alter the actions of epinephrine, the secreted adrenal medullary hormone of man produces the effects of pure epinephrine. The difference between the effects of the adrenal medullary hormone and of sympathetic innervation can

best be seen from Figure 4 which shows the actions of epinephrine and nor-epinephrine in a physiologic range (shaded areas). Speeding up of the total circulation and increase in muscle blood flow constitute the essential hemodynamic response to epinephrine. Aside from the well known hyperglycemic and calorogenic action of epinephrine, an increase of ACTH output and a subsequent increase of 11-oxy-steroid secretion occurs.

III. HYPERFUNCTION: PHEOCHROMOCYTOMA

Correlation of Clinical Features with the Catecholamine Content of the Tumors

No clinical syndrome corresponding to hypofunction of the adrenal medulla has been demonstrated. On the other hand the only known instance of hyperfunction in man is due to chromaffin tissue tumors; pheochromocytomas, which may originate in the adrenal medulla or wherever chromaffin tissue is found in the body during early life. The varying clinical syndromes observed in this disease can be grouped as follows: (1) paroxysmal hypertension (adrenal sympathetic syndrome); (2) persistent hypertension mimicking essential or malignant hypertension; (3) a combination of hypertension, hypermetabolism and glycosuria and (4) persistent hypermetabolism or hyperglycemia co-existent with intermittent hypertension.

The understanding of these widely varying syndromes has been helped by the demonstration that these tumors harbor two agents: epinephrine and nor-epinephrine in varying proportions.^{9,64} Added variables are the rate of secretion of the tumors and secondary endocrine and vascular (smooth muscle) changes.

If a functioning tumor of the adrenal medulla would resemble the mother organ, resting secretion would be negligible and a discharge of epinephrine and nor-epinephrine would occur only upon physiologic stimulation, e.g., by acetylcholine or histamine. This is partly true for a fraction of the cases studied, one-third according to Green⁶⁵ and one-fourth in our own series.²⁰ This classical type of pheochromocytoma is characterized by paroxysms (sometimes termed adrenal sympathetic syndrome) which are comparable to the effects of a rapid intravenous injection of a pharmacologic dose of epinephrine and/or nor-epinephrine. A steep rise of blood pressure, pallor, tachycardia, precordial and upper abdominal pain, hyperglyce-

mia and anxiety are the main features of this attack which may last for minutes or even hours. The attack then subsides or may lead to fatal pulmonary edema or ventricular fibrillation. The differences in the ratio of epinephrine to nor-epinephrine in these tumors should not

tinuous secretion of epinephrine and/or nor-epinephrine by the tumor.⁶⁹ This view is also supported by the large output of epinephrine and nor-epinephrine in urines of such patients.^{35,70}

Correlation of clinical and chemical data in this group²⁰ indicated that small tumors which

TABLE VI*
CORRELATIONS OF CHEMICAL AND CLINICAL FINDINGS IN TEN CASES OF PHEOCHROMOCYTOMA WITH PERSISTENT HYPERTENSION

No.	Name	Blood Pressure mm/Hg	Pulse Rate	Fasting Blood Sugar	BMR	933F Response	Weight of Tumor (gm)	Epi. mg/gm	Nor-epi. mg/gm	Epi. %	Nor-epi. %
10	S.M. NYH	170/110	130	245	not determ.	+	567	5.9	2.5	70%	30%
9	A.C. NYH	180/120	84	250	+21% +40%+7%	+	545 (½ blood)	6.52	1.27	84%	16%
6	M.E. PH	240/130	120	92	+38%	+	55	8.17	1.4	86%	14%
11	Z.Z. Mont.H.	240/140	84	282	+47%	+	39.5	7.65	2.02	79%	21%
7	D.N. MMH	214/138		120	(+64%)+1%	-		2.08	0.95	68%	32%
5	A.C. Pol.H.	190/130	80	167	+18%	+	62	3.6	4.1	47%	53%
8	A.S. PMH	170/120	100	135 diab. curve	not determ.	+		3.68	6.96	35%	65%
13	T.P. PH	130/100	140	222	not determ.	not determ.	180	0.44	3.2	12%	88%
12	N.B. BCH	240/130	72	120-140	+31%+52%	+	79	0.03	1.02	3%	97%
14	B.B. PH	180/115	88	not determ.	not determ.	not determ.	21	0.38	3.45	10%	90%
15	P.D. PH	Non-functioning thoracic phoe.						Adrenochrome only!			

* From GOLDENBERG et al., *Arch. Int. Med.*, 86: 823, 1950.

influence the clinical picture since large amounts of suddenly poured out epinephrine will cause over-all vasoconstriction just as nor-epinephrine does, while large amounts of nor-epinephrine will cause metabolic changes. (Fig. 4.) Little is to be gained from a study of these tumors toward an understanding of the normal function of the adrenal medulla. They reproduce rather the pharmacologic textbook picture of the effects of an epinephrine dose far above the physiologic range. Observations on cases which combine paroxysmal hypertension with persistent hypermetabolism or persistent hyperglycemia^{20,66,67} suggest that the "resting secretion" of these tumors may not be negligible but rather insufficient to produce pressure changes. This may well be due to the fact that metabolic effects are caused by much smaller doses of epinephrine than those required to produce hypertension.⁶⁸

More often pheochromocytoma is associated with persistent hypertension. The easily obtained adrenergic blocking effect in these cases suggests that this hypertension is due to con-

tained nor-epinephrine predominantly (90 to 97 per cent) and not more than a total of 80 mg. of this catecholamine gave a syndrome mimicking essential hypertension with unimpressive metabolic features. As the total amount of nor-epinephrine in the tumors increases, additional evidences of hypermetabolism and hyperglycemia are to be expected, although nor-epinephrine causes these to a much lesser degree than an equal amount of epinephrine. When the predominant catecholamine in the neoplasm was epinephrine hypertension, hypermetabolism, hyperglycemia and tachycardia occurred. (Table vi.)

A surprising observation was that patients with tumors containing large quantities of epinephrine may, at times, present a clinical picture indistinguishable from that of essential hypertensive vascular disease, with normal heart rate, absence of hyperglycemia, absence of metabolic disturbance as indicated by normal basal oxygen consumption and a negative or equivocal response to benzodioxane. This suggested that

persistent hypertension in patients with pheochromocytoma is not due at all times to the presence in the circulation of sufficient quantities of nor-epinephrine or epinephrine to cause hypertension by direct cardiovascular action, i.e., of the sort seen in the acute infusion experiment.²⁰

It appears that when significant amounts of either epinephrine or nor-epinephrine have been present in the circulation for long periods hypertension may be initiated which does not require these circulating agents for its maintenance ("secondary hypertension"). This view is supported by the fact that seven of our twelve patients with pheochromocytoma remained hypertensive for varying lengths of time after operative excision of their tumors. Whether this sustained hypertension is due to a specific action of epinephrine or nor-epinephrine or simply due to the fact that increases in blood pressure, if frequent in occurrence and of long enough duration, may persist longer than the stimuli which initiate them, is impossible to decide from presently available data.²⁰

Calkins et al.⁷¹ suggested that this "secondary hypertension" observed in pheochromocytoma may be due to chronic hypercorticism caused by chronic epinephrinemia. No clinical or pathologic evidence of hypercorticism was obtained in our cases. 17-ketosteroid excretion was found to be normal whenever examined. Only two instances of hypercorticism due to pheochromocytoma were found in the literature: The case of an infant, described by Neff et al.⁷² who showed the features of Cushing's disease and yet harbored a tumor which was found to be a pheochromocytoma on microscopic examination. No bioassay of the catecholamine content of the tumor was recorded. The second instance is an observation by Sprague⁷¹ who studied the urinary 11-oxysteroid and 17-ketosteroid excretion in a patient with pheochromocytoma and found both to be elevated.

Use of Pharmacologic Methods for the Diagnosis of Pheochromocytoma

Adrenergic Blocking Agents. Since pheochromocytomas as discussed above are more often associated with persistent elevation in blood pressure than with the more dramatic paroxysmal hypertension and since the clinical picture of these cases is often indistinguishable from that of essential and malignant hypertension, pharmacologic means have to be used to dif-

ferentiate these diseases. The bioassay of plasma for epinephrine and nor-epinephrine has only recently been perfected (Gaddum's modification of de Jalon's method)⁷³ but, even in the present form is hardly applicable to routine clinical use. Instead, adrenergic blocking agents can be used to demonstrate the presence of circulating epinephrine and nor-epinephrine. The adrenergic blocking action of benzodioxane (933F) was first used for this purpose in cases of pheochromocytoma by Goldenberg et al.⁶⁹ Whereas pheochromocytomas responded with a drop of systolic and diastolic blood pressure, hypertension of other etiology showed no change or a rise of blood pressure after intravenous administration of benzodioxane in doses of 0.25 mg./kg. It was surprising to find that the adrenergic blocking action occurred with nor-epinephrine as well, and tests performed on a patient who harbored a pheochromocytoma which contained, for practical purposes, only nor-epinephrine were highly positive on two occasions.⁷⁴ (Fig. 5.) This is in agreement with recent findings by Melville⁷⁵ who showed that the difference in response to epinephrine and nor-epinephrine following administration of adrenergic blocking agents is not apparent if the injection of the blocking agent occurs during an intravenous infusion of epinephrine or nor-epinephrine.

This diagnostic approach may fail in the "non-humoral" phase of hypertension in pheochromocytoma.²⁰ How frequently this type of hypertension occurs in pheochromocytoma is impossible to say at the present time. We know of five false negative tests and these were most likely due to this phenomenon. On the other hand, more than fifty-nine positive cases have been described in our recent summary.⁷⁴ Another limitation of the test seems to apply to results obtained in cases of hypertensive vascular disease with uremia in which four false positives are known to us. One of these cases observed by Grimson⁷⁶ showed also a positive response to another adrenergic blocking agent, the imidazoline derivative, regitine. It is also noteworthy that in this case fluorimetry gave evidence of hyperadrenalinemia.

More powerful adrenergic blocking agents such as dibenamine⁷⁷ and imidazoline derivatives⁷⁶ have been recommended for diagnostic use in pheochromocytoma. Their limitation for routine clinical use is due to the fact that they may also lower the blood pressure in some pa-

tients with essential hypertension.⁷⁸ No critical evaluation of the above mentioned tests will be attempted here. A recent careful analysis of this subject by Shapiro et al.⁷⁹ should be consulted.

Stimulants of Chromaffin Tissue Secretion. Since the local signs of the tumor are often negligible

combined with the use of an adrenergic blocking agent to make the test specific.

The histamine test was first suggested by Roth and Kvale⁸⁸ in 1945. They regarded as diagnostic a blood pressure rise which exceeds the cold pressor response significantly, i.e., a systolic rise of about 100 mm. Hg. False negative

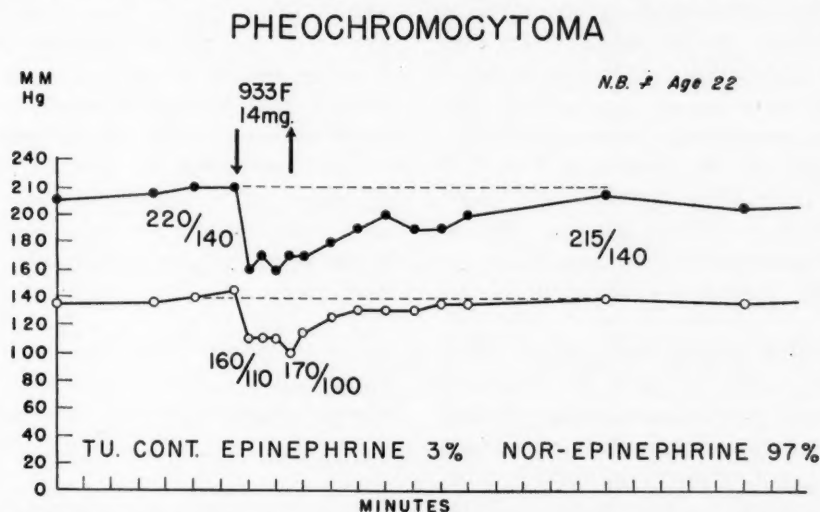


FIG. 5. Result of benzodioxane test in N.B., a hypertensive woman aged twenty-two, whose tumor contained 3 per cent epinephrine and 97 per cent nor-epinephrine. (From GOLDENBERG, M. and ARANOW, H., *J. A. M. A.*, 143: 1139, 1950.)

and since paroxysmal hypertension is not limited to pheochromocytoma, repeated attempts at a pharmacologic diagnosis of this variety have also been made. Adrenergic blocking agents cannot be used if normal blood pressure prevails between the attacks. An attempt has to be made to provoke discharge of epinephrine and/or nor-epinephrine stored in the tumor. It is well known that histamine,⁸⁰ acetylcholine which normally functions as transmitter at the synapses of the adrenal medulla⁸¹ and quaternary ammonium bases⁸² cause a discharge of epinephrine from the normal adrenal medulla. This can be convincingly shown in animal experiments only on intra-arterial injection of these substances into the stump of the celiac artery. It seems that a certain fraction of the tumors behaves like a denervated organ showing increased sensitivity to the above mentioned agents so that the intravenous injection of histamine (25–50 μ g. base), or the subcutaneous injection of mecholyl or the intravenous injection of tetraethylammonium chloride will be sufficient to cause a discharge of epinephrine and/or nor-epinephrine from the tumor. This will manifest itself in a striking hypertensive response which can be taken as evidence of a positive test in itself or be

responses have been reported and may be due to varying sensitivity of the tumors to this agent. Out of sixteen proven cases of pheochromocytoma twelve were positive and four false negative.⁷⁹ Nothing is known about the mechanism of false positive responses to histamine.⁸⁴

The use of mecholyl (25 mg. subcutaneously) as recommended by Guarneri and Evans⁸⁵ in 1948 should be preceded by a subcutaneous injection of atropine sulfate (1 mg.) in order to eliminate parasympathetic side effects, since the nicotinic effect of mecholyl on the adrenal medulla is not impaired by atropine.

Tetraethylammonium chloride which causes a blood pressure drop by ganglionic block in most cases of essential hypertension may produce a marked blood pressure rise in pheochromocytoma. It seems to us less likely that this is due to sensitization to circulating epinephrine and nor-epinephrine than to a discharge of these agents from the tumor. This test was first suggested by La Due et al.⁸⁶ in 1948. For a critical evaluation of the above mentioned tests the recent report by Shapiro et al.⁷⁹ may be consulted.

Urinary Excretion of Nor-Epinephrine and Epinephrine (Determination of Epinephrine and Nor-

Epinephrine by Bioassay). Normal human urine contains a mixture of catecholamines partly esterified (nor-epinephrine, epinephrine and perhaps hydroxytyramine).^{17,34,35} This mixture is roughly composed of 85 per cent nor-epinephrine with a small epinephrine fraction and approximates the composition of the sympathetic transmitter rather than that of the adrenal medullary hormone (70 to 90 per cent epinephrine). The daily excretion ranges from 15 to 45 μ g. nor-epinephrine in twenty-four hours.^{17,34,35} An excessive excretion of nor-epinephrine in essential hypertension (100–200 per cent above normal) as claimed by Holtz³⁴ was not confirmed.³⁵ Out of sixteen cases of essential hypertension only two showed an increased excretion (about 40 per cent above normal).

The determination of catecholamines in urine consists essentially of six steps:⁸⁷ (1) acid hydrolysis of a sample, (2) followed by adsorption of the catecholamines on aluminum hydroxide at pH 8,⁸⁸ (3) solution of the precipitate in acid, (4) removal of aluminum salts with alcohol and acetone, (5) evaporation of the alcohol and acetone, followed by (6) bioassay of the aqueous extract of the residue employing cat's blood pressure and rat's uterus.

The quantities of nor-epinephrine and epinephrine encountered in normal urines are too small to be determined by chemical means. A suitable method for the bioassay of nor-epinephrine (and epinephrine) is the cat's blood pressure. Chloralose anesthesia (60 mg./kg. i.p.) and cocaine sensitization (8 mg./kg.) have to be used to extend the range of the method down to about 0.2 μ g. of nor-epinephrine. The relative activity of l-nor-epinephrine as compared to l-epinephrine varies under these conditions between 2:1 to about 7:1. By the use of this method alone the potency of the urinary extracts can be expressed only as nor-epinephrine equivalent.

In order to determine the epinephrine content a modification of de Jalon's method as described by Gaddum⁷³ can be used. The rat's uterus is suspended in a modified Locke solution at a low temperature so that spontaneous activity is absent. Contractions are produced at regular intervals with acetylcholine and epinephrine estimated by the inhibition of these contractions. This method can usually determine 1 μ g. of epinephrine. Nor-epinephrine is 75 to 300 times less active in this test. From both determinations

the amount of nor-epinephrine and epinephrine present in the mixture can be calculated.⁸⁹

An increased urinary output of nor-epinephrine and epinephrine in pheochromocytoma was first described by A. Engel and U. S. von Euler.⁷⁰ This could be confirmed in two cases of pheochromocytoma in which the excretion of epinephrine and nor-epinephrine was far in excess of the values obtained in normals and hypertensives.³⁵ In one of these cases the daily excretion amounted to about 1,600 μ g. of epinephrine and 400 μ g. of nor-epinephrine. These values are based on determinations by both bioassay (cat's blood pressure and rat's uterus and colon) and paper partition chromatography of the urine extracts. The tumor weighed 43 gm. and contained:

Epinephrine.....	5.9 mg./gm.	77 per cent
Nor-epinephrine.....	1.85 mg./gm.	23 per cent

If the amount of epinephrine and nor-epinephrine secreted by the tumor is calculated from the urinary excretion in twenty-four hours (assuming that the percentage excreted in this way approximates that found in infusion experiments in man³⁶), the total output of the tumor in twenty-four hours is found to be about 80 mg. epinephrine and 20 mg. nor-epinephrine. This is compatible with the amounts of epinephrine and nor-epinephrine which would be necessary to maintain the pressure observed in this case.

Both cases observed³⁵ showed all the clinical characteristics of pheochromocytoma with persistent hypertension, hypermetabolism and hyperglycemia and repeatedly gave positive benzo-dioxane tests. This is also true for the two cases reported by Engel and von Euler.⁷⁰ Whether the urinary excretion is also increased in the "non-humoral" phase of persistent hypertension in pheochromocytoma,²⁰ which poses the major diagnostic problem, is under investigation. Nor-epinephrine and epinephrine determinations in urines as a diagnostic test for pheochromocytoma as suggested by Engel and von Euler⁷⁰ are hardly practicable if the present procedures necessary for catecholamine measurement in normal and hypertensive urines have to be employed. A simplified method involving direct concentration of a hydrolyzed urine specimen followed by bioassay on the cat's blood pres-

sure was recently suggested as a diagnostic procedure.³⁵

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Seminars on Pulmonary Physiology

Pulmonary Fibrosis and Respiratory Function*

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IT is the purpose of this paper to consider the influence of pulmonary fibrosis upon the function of the respiratory apparatus. As used in this discussion fibrosis is a generic term, connoting the proliferation of any or all of the components of fibrous connective tissue. It is a concomitant or sequel to most of the diseases of the lung and, depending upon its location, amount and histologic character, the fibrosis may or may not influence the nature and magnitude of associated physiologic alterations. Since proliferation of connective tissue is such a dominant part of many pulmonary diseases, one is justified in attempting to disclose its relationship to coexisting physiologic alterations in spite of the ambiguous nature of the problem. This can be done either by describing the physiologic alterations that have been observed in each specific disease that is known to be characterized by fibrosis, leaving to the reader the task of establishing whether or not there are histologic patterns that determine the changes in function, or one can make the attempt by setting forth those relationships that might be anticipated on the basis of *a priori* reasoning and then seek their confirmation in study of the diseased respiratory system. We have elected the second method, believing it to be more rewarding though perhaps less immediately useful and certainly less free from difficulty and error.

What technical limitations exist in this problem? Because fibrosis is usually accompanied by one or more other lung tissue reactions such as inflammation, edema, exudation, secretion, vascular engorgement and bronchial muscle spasm, each of which is capable of influencing pulmonary function, it is difficult to distinguish the effects of fibrosis *per se*. The scarcity of cases of pulmonary fibrosis that have been studied concurrently from both the histologic and physiologic standpoint is an addi-

tional handicap. For the most part we must rely upon the clinical identification of pulmonary fibrosis and it must be borne in mind that the antemortem identification of fibrosis is in reality a presumption, based largely upon previously established knowledge of the histologic characteristics of each particular pulmonary disease. In other words, the clinical recognition of fibrosis does not permit anatomic specificity. In addition, faults inherent in the methods available for quantitating cardiorespiratory function impair our ability to distinguish and grade dysfunction. Most of the methods available for these purposes are relatively insensitive and, in addition, certain technics that are adequate for studying undiseased individuals are less free from inherent fault when applied to diseased individuals. Far more hampering than the technical shortcomings of methods, however, is the fact that one rarely can study the same individual both before and during or after the development of fibrosis. Consequently, in order to distinguish evidences of quantitative or even qualitative abnormality of function one is forced to compare the data from the diseased individual with those of the statistically described normal man. Nearly all of the measurable activities of the respiratory apparatus demonstrate a wide quantitative variation among undiseased persons. Hence when a distinct anatomic abnormality is recognized in the lung, one often cannot be sure that it is or is not accompanied by an alteration of pulmonary function simply because the quantitative aspect of the specific function is so variable among normal persons. It is certain that these combined factors operate to lessen our acuity for discovering evidences of functional abnormalities in the presence of definite anatomic alteration.

A priori considerations suggest several ways in which fibrosis may interfere with respiratory

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and circulatory function. Fibrous tissue may destroy or replace previously destroyed lung tissue or it may by proliferation simply encroach upon the space that would normally be occupied by functioning lung tissue. In any event its mere existence presages a quantitative loss of functioning lung tissue. Moreover, since fibrous tissue of the relatively acellular collagenous and hyaline forms undergoes shrinkage or contraction, abnormalities of function due to the overdistention of coexisting normal lung tissue may develop. Fibrous tissue regardless of its location in the lung will limit the degree to which the involved parts of the lung can be distended. Its distribution may be *en bloc* or as cords that restrict the distensibility of that normal lung tissue which lies in the interstices. Fibrous tissue lying entirely outside the lung, as for example over the visceral or parietal pleura, and even in the respiratory muscles, thoracic joints or skin and subcutaneous tissues of the thoracic wall may act in the same binding fashion. Proliferation of the connective tissue of the bronchial mucosa or proliferation and contraction of fibrous tissue located either in or around the wall of the bronchi may narrow the lumen of the involved airways sufficiently to impede air flow. In addition, because of its resistance to stretch, fibrous tissue involving the bronchial system may interfere with air flow by diminishing the degree to which the airways are enlarged both as to diameter and length during the inspiratory phase of respiration. Fibrous tissue if appropriately located or present in large amounts can thus be expected to reduce or restrict the capacity and impair the pumping action of the respiratory apparatus. These abnormalities are evidenced by a reduction of the total volume of the lung and of the maximum breathing capacity.

When obstruction of the airways develops, one can anticipate that the alveoli distal to the obstruction will be inadequately ventilated and that the gases contained therein will have an abnormally high $p\text{CO}_2$ and low $p\text{O}_2$. The abnormal alveolar gas tensions may but will not necessarily be reflected by a parallel abnormality of these gases in the arterial blood. Whenever airway obstruction is focal so that normally ventilated alveoli coexist with those that are hypoventilated, two factors may reduce or even entirely prevent the occurrence of abnormal pulmonary blood gas exchange. If all of the venous blood flows through normally ventilated alveoli and those alveoli that are inadequately

ventilated are not at all perfused by pulmonary artery blood, there is no reason to anticipate interference with gas exchange except perhaps during the maximum rate of physical work. Although not strictly a part of *a priori* reasoning, the following comments seem best interjected here. Shunting of blood away from the capillaries of non- or poorly ventilated alveoli into those channels which perfuse the well ventilated alveoli is known to occur in diseased lungs. Evidence supporting this can be found in the fact that the $p\text{O}_2$ of arterial blood and also the degree to which arterial blood hemoglobin is saturated with oxygen are frequently observed to be within normal limits at rest and during exercise in the presence of lung disease which may be extensive. This must be interpreted as indicating either that little, or perhaps none, of the pulmonary artery blood flow perfuses the diseased areas, or that the diseased areas continue to be adequately ventilated and impose no abnormal barrier to the passage of gas from the air to the blood phase. The second interpretation is highly unlikely on the basis of the histologic abnormalities that are presumed to exist; moreover in some instances it has been demonstrated to be untenable by concurrent physiologic measurements demonstrating the arterial blood gases to be normal in the presence of inadequate rinsing (ventilation) of the lungs. Gross evidence of the shunt is repeatedly observed in those pulmonary angiograms that show an absence of the contrast media in the vascular bed of the diseased areas of the lung. The mechanism that shunts the blood away from the diseased areas is not always clear. Since the distribution of blood is governed by peripheral, intravascular resistance, the mechanism must be sought for in terms of this factor. In many instances the vascular bed of the diseased area is simply obliterated by thrombosis. This will not, however, explain all of the cases because postmortem injection has demonstrated patent vascular channels connected with the pulmonary artery in the diseased areas of some. The intravascular resistance to blood flow via these patent channels may be higher than that of those located elsewhere in the lung because of the local (diseased area) diminution of cyclic parenchymal enlargement during inspiration. It is also conceivable that the low $p\text{O}_2$ which is present in the non- or poorly ventilated alveoli may initiate a local constriction of the pulmonary artery radicles in a manner similar to or

identical with that described in the experiments of Dirken and Heemstra,^{1,2} since confirmed by others.^{3,4} The importance of the relationship between pulmonary artery circulation and alveolar ventilation is inadequately appreciated.

A second mechanism acting to diminish the seriousness of focal areas of hypoventilation involves the fact that the coexisting alveoli that are normally ventilated are sometimes actually hyperventilated. As a consequence the $p\text{CO}_2$ is abnormally low and the $p\text{O}_2$ slightly elevated in the gas of these hyperventilated alveoli. It is reasonable to postulate that the blood coming from the hyperventilated alveoli is lower in CO_2 and slightly higher in O_2 content than that blood which comes from the hypoventilated alveoli, and that the one offsets the other thus tending to neutralize the undesirable effects of focal alveolar hypoventilation. When the well ventilated alveoli far outnumber those that are poorly ventilated, complete blood gas compensation can occur. For obvious reasons this mechanism is far more effective in regard to CO_2 than to O_2 .

Quite aside from its effects upon the ability of the respiratory apparatus to move and distribute air, fibrosis may impede the transfer of oxygen and carbon dioxide between the blood and gas phase in a direct manner by altering the tissue barrier through which oxygen and carbon dioxide must pass in moving between the blood and gas phase of the alveoli. Proliferation of the connective tissue that supports the alveolar vascular bed not only increases the distance that must be traversed by each molecule of gas but also changes the character of the medium. Under such conditions, even though the $p\text{O}_2$ and $p\text{CO}_2$ of alveolar air may be normal, venous blood perfusing the alveolar capillaries thus involved may be incompletely arterialized. Because of the fact that O_2 diffuses through tissue less readily than does CO_2 the altered barrier will impede the passage of oxygen to a much greater degree than it will that of carbon dioxide. The extent to which such abnormal segments are perfused with pulmonary artery blood will determine the degree to which the systemic arterial blood is altered. If normally functioning pulmonary units exist elsewhere in the lung, the pulmonary artery blood may be shunted away from the abnormal and entirely into the normal units and under such circumstances no abnormality of the systemic arterial blood will be discoverable.

The vascular bed of the pulmonary artery may be affected directly or indirectly by pulmonary fibrosis. Thrombosis of the major pulmonary arteries or subdivisions thereof may occur discretely or as a part of fibrosis of the pulmonary unit. Perivascular fibrosis of the arterioles, capillaries or venules, even in the absence of actual thrombosis, may limit the distensibility of the vascular bed and thereby interfere with the physiologic enlargement it is known to undergo during exercise. Fibrosis causing emphysema indirectly but no less definitely influences the vascular bed. The capillaries of the enlarged alveoli are narrowed and lengthened and when the alveolar septa finally rupture the capillaries are destroyed. In addition, the capillaries of those alveoli that are overdistended by a high intra-alveolar pressure (obstructive emphysema) may be subject to compression by the intra-alveolar force. Depending on the extent to which the vascular bed is destroyed or compromised by fibrosis one can anticipate an impediment to the flow of blood through the lesser circulation and, under conditions of stress, pulmonary artery hypertension with its effects upon the circulatory system may develop. The interference with blood flow consequent to fibrosis also explains in part the shunting of blood away from diseased and into healthy units of lung tissue. It is also conceivable that obliteration or restriction of the vascular bed may so severely reduce the area of the diffusion surface as actually to interfere with proper gas exchange. In other words, during stress the velocity of blood flow through the restricted capillary bed may be so great as to allow insufficient time for adequate transfer of oxygen and carbon dioxide. It is also possible that the diffusion surface may become so restricted that the volume of blood in the alveolar capillaries may be too large for complete oxygenation, either on the basis of a volume of blood to volume of gas ratio or because the cross section area of each capillary becomes too great to permit oxygenation of the axial cells during the time they pass by the diffusion surface.

One additional possible effect of fibrosis must be discussed. It is known that nerve endings within the lung, pleura and muscles and joints of the thoracic bellows send impulses to the spinal cord and higher centers which arise in response to changes of tension in the surrounding tissue. Pulmonary fibrosis may either so alter the state of the tissues surrounding these

nerve endings, or may so change the pressure brought to bear upon them, that the central nervous system is bombarded by an unusual pattern both as to magnitude and frequency of stimuli. Some of the specific clinical manifestations of pulmonary fibrosis can be explained best by invoking such a mechanism. These

quacy; (4) the production of unusual stimuli originating in the respiratory apparatus and passing to the brain.

METHODS

The methods used in measuring the various aspects of pulmonary function of the cases herein

Table I
PULMONARY VOLUMINA, VENTILATION EFFICIENCY, MAXIMUM BREATHING CAPACITY AND FLUOROSCOPY

Case No.	Total Volume		Vital Capacity		Residual Air		Residual Air Total Volume x 100 (%)	Terminal Alveolar Nitrogen	Maximum Breathing Capacity			Speed of Emptying
	Pre-dicted	Deter-mined	Pre-dicted	Deter-mined	Pre-dicted	Deter-mined			Pre-dicted	Deter-mined	ABD*	
I	4.64	3.88	3.72	3.00	0.92	0.88	23	1.47	150 [†]	124	-	Normal
II	5.22	6.06	3.95	4.81	1.18	1.25	21	1.16	161	204	-	Normal
III	6.40	6.84	4.84	4.56	1.56	2.28	33	1.94	140	156	-	Normal
IV	4.54	3.94	3.43	2.79	1.11	1.15	29	1.10	146	100	94	Slow
V	5.80	5.67	4.39	3.07	1.41	2.60	46	1.60	117	45	56	Very slow
VI	6.24	5.57	4.72	2.11	1.52	3.46	62	2.9	137	31	42	Very slow
VII	4.53	4.75	3.42	3.15	1.11	1.60	34	6.34	156	116	120	Trapping right lung
VIII	5.10	3.90	3.86	2.75	1.24	1.15	30	0.88	122	138	135	Normal
IXa	4.34	2.45	3.48	1.94	0.86	0.51	21	1.3	165	68	68	Normal
IXb	4.34	3.85	3.48	2.94	0.86	0.91	24	2.0	165	130	-	Normal

* After bronchodilator

† See text, Case I

unusual patterns of stimulation lead to a rate of breathing in terms of cycles and liters per minute which is out of proportion to the amount of physical work being done. Moreover, these abnormal stimuli may go all of the way to the cerebral cortex and thus contribute directly to the actual sensations of breathing distress.

It is apparent from these *a priori* considerations that, depending upon the location, amount and character of the change, fibrosis can be expected to: (1) reduce the total capacity of the lung; (2) interfere with the action of the apparatus as an air pump by increasing the resistance to air flow in the bronchial system or by restricting the motion of the thoracic bellows; (3) interfere with proper ventilation of the alveoli and (4) reduce the absolute size and distensibility of the pulmonary artery vascular bed. These anatomic alterations in turn may lead to: (1) a reduction of the breathing ability; (2) inadequate ventilation of the venous blood as evidenced by arterial hypoxia and hypercapnia; (3) pulmonary artery hypertension and consequent cor pulmonale and circulatory inade-

quacy; (4) the production of unusual stimuli originating in the respiratory apparatus and passing to the brain.

Maximum breathing capacity (Table I) determined as described by Hermannsen.⁶ The predicted value for the normal man is calculated according to the regression formula obtained by Wright⁷ from a study of 135 normal men between the ages of twenty-five and sixty-five years and is as follows: Maximum breathing capacity = Height in centimeters \times (1.24 - 0.0095 \times age in years) \pm 17.5 L.

Pulmonary volumina (Table I) determined by a slight modification of the open circuit method described by Darling et al.⁸ The predicted values are calculated from the regression formula of Kaltreider et al.⁹ using the radiologic chest volume.

Arterial blood gas (Table II): The blood samples both at rest and during exercise on the treadmill were obtained through an indwelling needle using heparinized syringes. The blood gas contents were measured according to the technic of Van Slyke and Neill¹⁰ and the oxygen capac-

ity by the method of Sendroy.¹¹ The gas tensions were measured directly by a modification of the original technic of Riley et al.¹² to be published by Filley et al.¹³

Alveolar pO₂ and the alveolar-arterial oxygen difference (Table II): The alveolar pO₂ was calculated

speed of the mill is kept constant, never more than 3.5 miles per hour, but the grade is increased at each successive walk until a stint that cannot be tolerated for six minutes is reached. In a study of forty normal men between the ages of twenty-five and sixty years Wright et al.¹⁵

Table II
ARTERIAL BLOOD GASES, PARTIAL PRESSURE OF OXYGEN IN THE ALVEOLI AND DIFFERENCE BETWEEN THE PRESSURE OF OXYGEN IN THE ARTERIAL BLOOD AND ALVEOLI

Case No.	Blood Sample Withdrawn	Carbon Dioxide Content vol. %	Oxygen Content vol. %	Oxygen Capacity vol. %	Hemoglobin % Saturation	pH	pCO ₂ mm. Hg	pO ₂ mm. Hg	Alveolar pO ₂ mm. Hg	Alveolar-Arterial Oxygen Difference mm. Hg	Oxygen Uptake per Minute (L.)
I	(At rest)	49.27	15.48	16.10	96.1	7.45	41	82	96	14	0.25
I	(During 6th minute of exercise)	37.52	15.98	16.97	94.2	7.40	39	84	104	20	1.24
II	(During 6th minute of exercise)	38.84	21.11	21.80	97.0	7.36	39	88	104	16	*1.95
III	(During 6th minute of exercise)	41.76	18.69	19.78	94.5	7.38	39	72	99	27	2.09
IV	(At rest)	48.41	19.31	20.97	92.0		37	80	97	17	0.20
IV	(During 6th minute of exercise)	42.67	19.21	21.28	90.0		37	72	100	28	1.70
V	(At rest)	45.39	20.42	22.37	91.0		44	79	87	8	0.30
VI	(At rest)	45.30	19.21	20.15	95.0	7.41	41	81	96	15	0.32
VI	(During 4th minute of exercise)	54.33	17.98	20.66	87.0	7.43	48	60	74	15	0.81
VII	(During 4th minute of exercise)	40.88	15.17	17.00	89.0						1.05
VIII	(At rest)	44.35	20.26	21.86	92.7	7.48	35	67	104	37	0.32
VIII	(During 6th minute of exercise)	41.84	15.78	23.14	68.2	7.45	41	33	97	64	0.88
IX	(During 4th minute of exercise)	39.00	19.15	20.70	93.0						1.10

In our laboratory, the mean and standard deviations for arterial blood characteristics during strenuous exercise by normal males is as follows: Carbon dioxide content = 42.00 ± 4.55 vol. per cent; hemoglobin saturation = 94.93 ± 2.33 per cent; pH = 7.39; pCO₂ = 38.00 ± 3.98 mm. Hg; pO₂ = 82.5 ± 5.41 mm. Hg; alveolar pO₂ = 102.1 ± 5.07 mm. Hg; alveolar-arterial oxygen difference = 19.60 ± 4.74 mm. Hg.

according to Equation 12 in the paper by Riley and Cournand.¹⁴ The alveolar-arterial oxygen difference is simply the difference between the calculated alveolar pO₂ and the directly determined arterial pO₂.

Exercise data (Table III): All exercise was done on a motor driven treadmill, the expired air being collected in the fifth and sixth minutes of exercise. O₂ and CO₂ content were measured by the Haldane apparatus and the calculations of gas exchange made in the conventional manner. Pulse rate was recorded electrically and respiratory rate mechanically.

Maximum O₂ consumption: The O₂ uptake during the fifth and sixth minutes of exercise on the treadmill during the severest intensity of work tolerated for six minutes is measured in the manner just mentioned. In each walk the

have found the predicted normal peak value of O₂ uptake to fit the regression formula: O₂ uptake in liters per minute per square meter of body surface = $1.855 (0.0104 \times \text{age in years})$. The standard deviation from the mean in this study is 0.185 L.

Bronchspirometry (Table IV) performed as described by Wright and Michelson.¹⁶

DISCUSSION OF CASES

As mentioned previously, it is difficult to distinguish the physiologic effects of fibrosis *per se* because of coexisting histologic changes such as inflammation, edema, vascular engorgement, etc. In addition, one rarely has an opportunity to study any single pattern of fibrosis in a pure form. The cases presented herein have been chosen because they represent for the most

part a single pattern or known combinations of patterns of connective tissue proliferation. That the data must be considered with due regard to other histologic alterations is obligatory. In some instances there may be disagreement in designating the histologic pattern of these cases

customarily considered forms of pulmonary fibrosis.

Case I is that of a sixteen year old white male who developed an acute lobar pneumonia which did not resolve on antibacterial therapy and was ultimately determined to be tuberculous in

Table III
RESPIRATORY, METABOLIC AND CIRCULATORY RESPONSE TO EXERCISE

Case	I	Ila	Ilb	III	IVa	IVb	V	VI	VII	VIII	IXa	IXb
Ventilation, L. per minute at 37° C.	57.4	62.8	125.0	78.4	45.3	83.5	42.3	21.1	44.0	76.3	40.0	36.4
Breaths per minute	50	32	56	30	26	40	36	36	-	68	-	-
Tidal air, L. at 37° C.	1.15	1.97	2.22	2.62	1.75	2.04	1.06	0.58	-	1.12	-	-
Oxygen uptake, L. per minute STPD	1.43	2.10	2.51	2.55	1.71	2.30	1.45	0.90	1.05	1.00	1.10	1.15
Carbon dioxide output, L. per minute STPD	1.42	2.17	3.05	2.95	1.71	2.76	1.26	0.57	0.99	0.98	0.96	1.01
O ₂ V ^x	40.0	29.9	50.7	30.8	26.5	36.4	29.2	23.5	42.0	76.3	36.4	31.7
V.M. M.B.C. x 100 ^y	46	31	61	50	46	85	94	68	39	55	59	28
Dyspnea according to patient	2+	1+	4+	4+	1+	4+	4+	4+	2+	4+	4+	0
Maximum oxygen uptake ^z :												
Predicted	-	-	1.47	1.34	-	1.45	1.30	1.325	-	1.252	1.626	-
Determined	-	-	1.28	1.27	-	1.34	0.78	0.45	-	0.53	0.65	-
Pulse Rate, last minute exercise	192	-	-	172	152	178	152	128	-	140	-	126
Pulse rate, 10th minute recovery	152	124	136	104	104	104	116	84	-	100	-	78

^x Oxygen ventilation equivalent = Ventilation per minute in L. at 37° C.
Oxygen uptake per minute in L. STPD

^y Ventilation per minute in L. at 37° C. x 100 = Index of dyspnea
Maximum breathing capacity

^z Oxygen uptake in L. (STPD) per minute per square meter of body surface during maximum tolerated work. Standard deviation from the mean = 0.185

Table IV

PROPORTION OF RESPIRATORY FUNCTION ACCOMPLISHED BY EACH LUNG MEASURED DURING THE RESTING STATE BY BRONCHOSPIROMETRY

	Case I (%)	Case VII (%)	Case IXa (%)	Case IXb (%)
Right Lung:				
Ventilation	55	19	30	48
Oxygen consumption	77	6	15	45
Carbon dioxide output	62	5	20	48
Vital capacity	73	-	12	46
Left Lung:				
Ventilation	45	81	70	52
Oxygen consumption	23	94	85	55
Carbon dioxide output	38	95	80	52
Vital capacity	27	-	88	54

as "fibrosis" even by the broad definition given earlier. From a clinical point of view they are

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character. The chest roentgenogram, shown in Figure 1, taken six months after onset of the illness revealed a massive consolidation of the upper portion of the left lung, the mediastinum being displaced to the left and the left hilum elevated. Bronchoscopy disclosed nothing abnormal other than slight distortion upward of the left main bronchus. When the left hemithorax was opened surgically, the left upper lobe was noted to be firm and extensively adherent to the chest wall. The superior segment of the left lower lobe was also firm. The upper lobe and superior segment of the lower lobe were resected. The pathologist described the upper lobe as being normal in size for a collapsed upper lobe. It was solid except for the lingula which contained numerous firm nodular masses and was congested. Histologically there was extensive tuberculosis in all phases of development, with numerous cavities measuring approximately 2.5 cm. The lung tissue which was not destroyed

by the tuberculous process was the site of lipoid pneumonia and there were numerous blood-containing patent vessels in the fibrocaseous and pneumonic tissue.

This case exemplifies massive necrosis, caseation and fibrosis of tissue quite sharply confined to approximately one-half the left lung. The remainder of the left lung appeared normal in all respects to the surgeon and there is no evidence of disease in it or in the right lung on the roentgenogram. The total volume and vital capacity as shown in Table I were significantly less than the predicted normal values but the residual air was not increased nor was there evidence of impaired rinsing of the lung, the terminal alveolar nitrogen being less than 2 per cent. Because our data in men younger than twenty-five years of age are inadequate, we do not know what the correct predicted normal value for maximum breathing capacity should be in this case. Our sparse data indicate that males under twenty-five years of age have a smaller maximum breathing capacity than do those who have attained the age of twenty-five. The figure of 150 L. recorded in Table I is a rough estimate. It is probable that the maximum breathing capacity of this patient was subnormal. The alveolar-blood gas relationships were, as shown in Table II, observed to be normal both at rest and during exercise. It is obvious therefore that little if any of the output from the right ventricle perfused the diseased lung tissue. The mechanism whereby the blood was diverted from the diseased lung is not clear. In the fibrocaseous areas many of the capillaries were undoubtedly destroyed; nevertheless patent, blood containing channels persisted, especially in the areas of lipoid pneumonia. It is impossible to determine by the technics used whether or not these vessels all had a direct connection with the pulmonary artery but it can safely be presumed that those capillaries located in recognizable alveolar septa did have. It is entirely possible, however, that the blood seen in the alveolar capillaries actually came from the bronchial arteries by way of the functional anastomoses that are known to develop in chronic suppurative disease. Our blood gas data can be interpreted only as indicating little or no flow of right ventricular blood through the capillaries but the mechanism accounting for this is purely speculative and was discussed under *a priori* considerations.

The extent to which each lung participated

in respiration at rest is shown in Table IV. Although the left lung participated to a normal extent in ventilation during quiet breathing it was, as is shown by the partition of vital capacity, markedly restricted during a deep breath. A comparison of roentgenograms taken at full inspiration and full expiration suggested that the change in size of the left hemithorax was less than that of the right. Planimetry confirmed this observation showing that only 37 per cent of the total thoracic change occurred on the left side. The unilateral limitation of thoracic motion plus the shift of the mediastinum to the left during a maximum inspiration accounts for the reduction in vital capacity of the left lung as measured by bronchspirometry. Since by bronchspirometry the left lung was shown to participate to a normal degree in quiet respiration, one must conclude that the limitation of thoracic motion occurred only during more strenuous breathing efforts. The extensive adhesions between the upper lobe and the chest wall will not entirely explain the limitation of chest wall motion because there was no restricting pleural membrane and the lower lobe and diaphragm were free of adhesions. Further explanation may be found in the fact that only the lower lobe, and not all of it, could expand during inspiration. It can safely be assumed that the left lower lobe, being too small to fill properly the space created by thoracic motion, rapidly reached its limit of distention during inspiration and resisted the centrifugal motion of the left chest wall and diaphragm. Some additional motion of the parietes was achieved by pulling the mediastinum to the left.

Equally striking was the disproportion between the ventilation and oxygen uptake of the left lung. Since in this case the arterial hemoglobin is known to have been normally saturated with oxygen, that portion of the entire oxygen uptake of the body which was accomplished by each lung is therefore a direct measure of the proportion of the right ventricular output that flowed through each lung. In this case approximately 23 per cent of the right ventricular output perfused the left lung and is essentially the amount that one would anticipate with only the left lower lobe functioning.

This case presents an interesting study in compensatory mechanisms. During quiet breathing the left lower lobe was apparently entirely capable of going through cycles of volume change that were double or more its normal excursions.

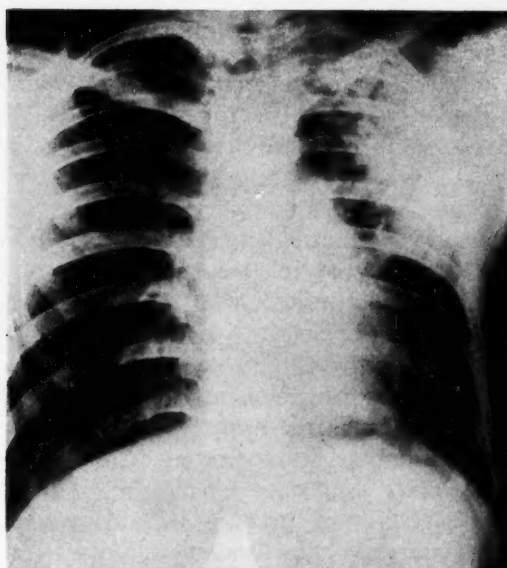


FIG. 1. Case 1. Roentgenogram of chest; full inspiration.

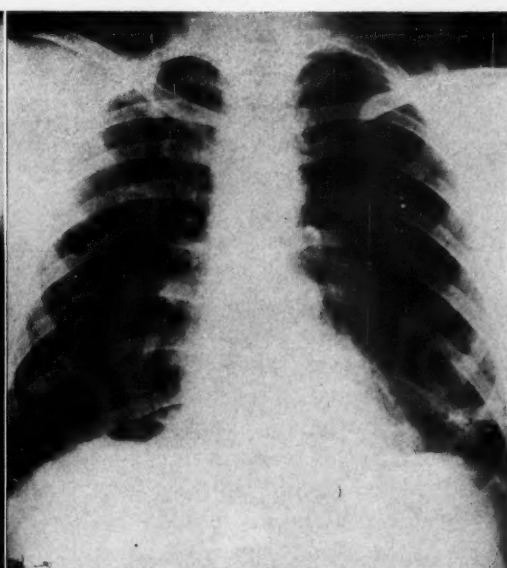


FIG. 2. Case 11. Roentgenogram of chest; full inspiration.

Therefore, during quiet breathing the left lower lobe could adequately substitute for the entire left lung in so far as breathing was concerned and showed evidence of inadequacy in this respect only during deep breaths. There does not appear to be similar compensation in respect to blood flow through the vascular bed of the left lower lobe. Apparently the peripheral resistance of the vascular bed in the functioning lobe on the left underwent little if any decrease and blood flow therefore did not increase parallel with ventilation. It may actually have decreased. Since hyperventilation of normal alveoli will not of itself appreciably increase O_2 uptake, because of the chemical nature of hemoglobin, oxygen uptake in this case did not increase parallel with ventilation. CO_2 output depends, however, on the alveolar pCO_2 and, since this can be lowered by hyperventilation, the CO_2 output can be augmented by the hyperventilated alveoli. This is shown in Table IV by the fact that the CO_2 output of the left lung in Case 1 much more nearly approximated the ventilation than it did the oxygen uptake. Compensation, if one wishes to call it that, was during quiet breathing complete as regards minute ventilation, incomplete as regards CO_2 output and non-existent as regards O_2 uptake. During deep breathing compensation was lacking in respect to ventilation. There are no data concerning the circulation-ventilation relationships in such a lobe during exercise. The right or opposite lung in this case was of course over-

perfused with blood in respect to its ventilation. During quiet breathing the blood leaving it was probably normally saturated with O_2 , although on theoretic grounds it would be slightly lower in pO_2 and would be slightly higher in CO_2 both as to content and pCO_2 . The bronchspirometric data in this case are typical of the uncomplicated overdistended lung.

The respiratory and pulse response to moderate exercise of six minutes' duration, as shown in Table III, was abnormal in that the respiratory rate was unusually rapid and the minute ventilation was, as shown by the high O_2V , larger than the normal value for the work load as represented by the O_2 consumption. Arterial hypoxia or hypercapnia cannot be invoked to explain the pattern of overbreathing. This patient was mildly febrile, ill and slightly debilitated though he had not been confined to bed for more than a few days at the time of our study. It may be that as yet unknown factors associated with his general physical condition influenced the respiratory pattern. It is equally possible that stimuli originating in the overstretched lower lobe, in the semirigid upper lobe, in the shifting mediastinum, or in the chest wall itself may have brought about the abnormal respiratory pattern.

In summary, Case 1 shows evidences of loss of functioning lung tissue and of overexpansion of the remaining lung tissue on the side of the disease. (Fig. 1.) Pulmonary artery blood was shunted away from the diseased lung substance.

The physiologic data are typical of those seen in extensive destruction and fibrosis limited to one side and not complicated by disease in the remaining lung tissue. The findings agree with those that are predicted on the basis of *a priori* reasoning.

Case II is a thirty-seven year old white male, who had a chest roentgenogram taken in August, 1948, because his sister was discovered to have active tuberculosis. This roentgenogram was interpreted as being negative. A routine follow-up roentgenogram, taken in April, 1950, however, was interpreted as revealing abnormal densities scattered throughout both lungs. There were no symptoms at this time but in June, 1950, he had mild pleuritic and substernal pains. The roentgenogram of the chest made in September, 1950, at the time of our studies is shown in Figure 2. At that time physical examination of the patient revealed nothing abnormal. In October his right hemithorax was opened surgically and a section of the right upper and middle lobe was removed for histologic examination. Palpation of the entire lung at the time of operation revealed it to be seeded with well defined nodules up to 2 cm. in size. Histologically, the lung revealed discrete lesions varying in size and described as a mass of central dense fibrosis with thick interlacing non-whorled collagen strands surrounded by many small epithelioid cell tubercles without caseation. Occasional similar tubercles occur within the central scarred zone. Some of the lesions embraced bronchioles and all contained patent vascular channels. These latter were relatively few in number. The intervening lung tissue was described as being entirely normal in appearance. The histologic diagnosis was Boeck's sarcoid. The pulmonary volumina as shown in Table I were normal, as was also the maximum breathing capacity. There was no evidence of impaired lung rinsing, the terminal nitrogen being less than 2 per cent. The arterial blood gases and the difference between the alveolar and arterial pO_2 were, as shown in Table II, within normal limits. The respiratory response to moderate exercise, IIa in Table III, was entirely normal. During the most severe exercise of which the subject was capable, IIb in Table III, the response was probably abnormal in that overbreathing as indicated by the high O_2V was very pronounced. Normal individuals can augment respiration to a greater degree than oxygen uptake during exercise and, for this reason, the

oxygen ventilation equivalent (O_2V) tends to be higher during maximum work than during moderately severe exercise. We have insufficient data describing the range of the O_2V during maximum exercise in normal subjects but such data as we do have contain no ventilation equivalent greater than 36. It appears that the ventilation equivalent under maximum stress was abnormal in this subject. An additional abnormality noted was the persistently high pulse rate at the 10th minute of recovery. The same comments made regarding the stimulation of the respiratory center and the pattern of breathing in Case I apply also in this case. The abnormal pulse response cannot be readily explained but may be on the basis of direct involvement of the myocardium by sarcoid.

Case III is a forty-nine year old white male, who has worked for twenty-five years as a metal miner and whose exposure to the inhalation of crystalline free silica was moderately severe during the first fifteen years. During the past ten years he has had relatively little exposure to fine particles of quartz although he has continued in his occupation as a miner doing strenuous work. Roentgenograms of the chest taken ten years ago reveal discrete nodulation distributed evenly throughout both lungs. During the ensuing years the nodules have become slightly more pronounced as to size, number and definition of border. At the time of the physiologic measurements he had no complaint other than that of being "short of wind" if he climbed rapidly. He could climb 150 steps on a 45 degree rise at a moderate rate without stopping. He had a non-productive morning cough and smoked twenty cigarettes daily. Physical examination of this patient revealed nothing abnormal. The present roentgenogram of the chest is shown in Figure 3. The pulmonary volumina, maximum breathing capacity and efficiency with which the lung could be rinsed were all, as shown in Table I, within normal limits. The same is true of the arterial blood gases shown in Table II and response to exercise shown in Table III. No histologic material is available from this case: in fact, none has been obtained from any of our moderately large series of discrete nodular silicosis at an interval of less than four years after our physiologic studies.

These two cases of discrete disseminated fibrosis may surprise some as regards to the normality with which the respiratory apparatus

functions. In Case II we know that the lung tissue not directly involved by the disease was normal in appearance. One cannot estimate the total volume of fibrosis represented by the nodules in aggregate but the mass was apparently not large enough to interfere mechanically with respiratory function.

Gardner¹⁷ has pointed out that in uncomplicated discrete nodular silicosis the alveoli immediately around the nodule are distorted and dilated and that the intervening lung tissue usually shows a recognizable degree of emphysema. He also states that there are great numbers of apparently sound alveoli and associated capillaries. It may be presumed that Case III is a typical silicotic and that his lung would be as described by Gardner. The ratio of residual air to total volume in Case III is at the upper limits of normal, as is also the difference between the alveolar and arterial pO_2 . These may represent true deviations from normal for this individual but in any event they are not striking and are less severe than one might have anticipated on the basis of the presumed histologic alteration. It is pertinent to recall that our methods and opportunities for discovering deviations from normal function suffer from the handicaps mentioned earlier. Perhaps those interested in pathology will not think it impertinent for us to suggest that the histologic diagnosis of emphysema also is beset by some difficulties.

In summary, both of these examples of discrete disseminated fibrosis have retained essentially normal respiratory function. Their peak ability for oxygen uptake, a measure of integrated physical prowess, was within one standard deviation of the mean of the predicted values.

Case IV is a thirty-nine year old white male metal miner, who sustained a heavy exposure to crystalline free silica between 1928 and 1934 but has had none since that time. His first chest roentgenogram showed nodular densities distributed throughout both lungs with slight coalescence in the upper third of both lungs. Since 1934 he has had frequent chest colds and several attacks of pneumonia. At the time of our study he complained of being short of breath if he climbed more than one ordinary flight of stairs at a moderate rate. His performances in and around the laboratory did not confirm this complaint. The roentgenogram of the chest, taken at the time of our physiologic measure-

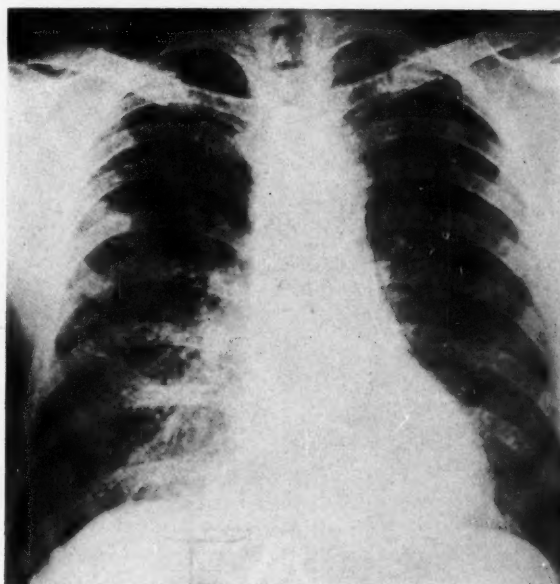


FIG. 3. Case III. Roentgenogram of chest; full inspiration.

ments is shown in Figure 4. They reveal massive conglomerate densities in the upper portion of both lungs with nodules scattered throughout the remainder of the lungs. The expiration film shows normal excursions and density change.

Case V is a 57 year old white male metal miner, who had approximately twenty-five years of exposure to various concentrations of crystalline free silica. During the past ten years, though continuing his work as a miner, he has had very little further exposure to finely particulate quartz. At the time of our study his roentgenogram was as shown in Figure 5. He complained of a chronic cough productive of a tablespoon of white tenacious sputum daily. The sputum was very difficult to "raise." He stated that he could scarcely climb a flight of stairs, even at a slow rate, and that he could not exceed a moderate pace on the level. This was confirmed by his actions about the laboratory. In spite of his complaints he was able to put in a full eight-hour day underground, primarily as a foreman of ordinary labor. This occupation permitted him to walk slowly and to spend a considerable part of his time standing quietly or sitting.

Cases IV and V are examples of combined massive and discrete disseminated fibrosis which may be classified as conglomerate silicosis. They offer an interesting contrast that is observed fairly often in silicosis. Case IV had, as shown in Table I, a normal total volume, residual air and terminal nitrogen, thus failing to exhibit

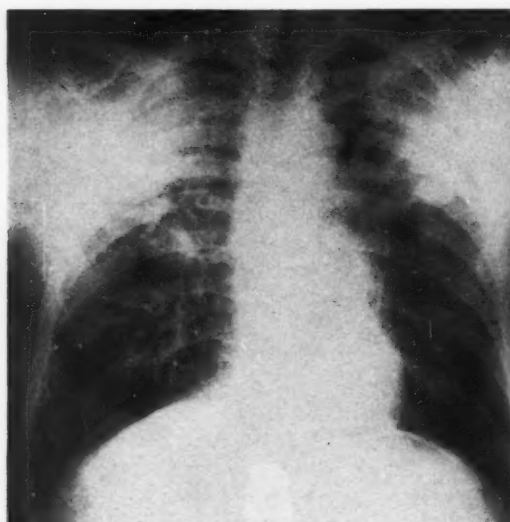


FIG. 4. Case iv. Roentgenogram of chest; full inspiration.

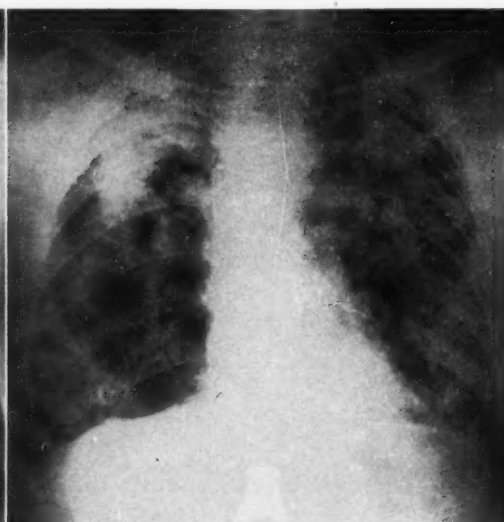


FIG. 5. Case v. Roentgenogram of chest; full inspiration.

the abnormal evidences commonly observed in diffuse obstructive emphysema. The subnormal maximum breathing capacity and slow speed of expiration observed fluoroscopically most likely indicate an element of impediment to air flow through the bronchial passages. In addition, Case iv had a normal work capacity as evidenced by the normal peak of oxygen uptake shown in Table III. In contrast, Case v does show evidences of moderately severe obstructive emphysema in that the residual air is definitely increased and the maximum breathing capacity is markedly diminished. The normal terminal alveolar nitrogen of Case v (obtained in duplicate runs) is not particularly unusual in our experience despite the abnormal pulmonary volumina. As shown in Table II, Cases iv and v may have very slight arterial hypoxia and Case v perhaps even a slight retention of CO_2 . It is possible in both cases that pulmonary artery blood perfuses some vessels that are located in thickened alveolar septa or imbedded in fibrous tissue. It is also possible that, as pointed out by Comroe,¹⁸ the terminal alveolar nitrogen is not an entirely adequate index of the effectiveness with which the lung is rinsed and that poor alveolar ventilation may actually account for the blood gas changes of these two cases. As might be anticipated Case v, as shown in Table III, had a much lower maximum ability for oxygen uptake than did Case iv. Because of his low maximum breathing capacity Case v became intolerably dyspneic when breathing 42 L. of air per minute whereas Case iv was able to go on until he breathed

83.5 L. per minute before respiratory distress became intolerable. Neither case showed any evidence of overbreathing during exercise, the difference in their work capacities being accounted for solely by the difference in their maximum breathing capacities. The respiratory pattern also differs at similar rates of oxygen uptake during exercise, as can be seen in Table III by comparing Case iva working at a moderate intensity to Case v working at peak capacity. Case v, having a smaller vital capacity, attained a minute ventilation equal to that of Case iv by breathing at a faster rate. An abnormally high respiratory rate and small tidal volume during exercise is characteristic of persons having moderately severe emphysema or airway obstruction. Both of these cases show an additional feature that characterizes diffuse airway obstruction. The normal man at the peak of severe exercise will not use more than 60 per cent of his respiratory power as measured by the maximum breathing capacity whereas most persons with diffuse airway obstruction will use 90 per cent or more. Sometimes in the latter cases the minute ventilation during maximum exercise actually considerably exceeds the maximum breathing capacity measured in the conventional manner. Several factors are involved in this phenomenon. First, in the normal man the circulatory and not the respiratory system limits the maximum of oxygen uptake during physical work. Hence as long as the circulatory system retains its powers a diminished maximum breathing capacity will be used to a greater than

ordinary extent. Second, in emphysema air flow through the obstructed airways can be augmented to a rather fixed degree and then, regardless of the additional force used, the flow of air will not be further accelerated. In fact further augmentation of respiratory force seems to exaggerate the obstruction. This has been demonstrated experimentally¹⁹ in our laboratory by showing that equal maximum breathing capacity values are obtained in a case of airway obstruction during both moderate and very severe efforts. Third, there is the possibility that exercise alters the condition of the respiratory apparatus. The maximum breathing capacity measured during exercise or immediately afterward is sometimes larger than before exercise.

Lacking histologic study of these two cases one must assume for purposes of discussion that they would both show the classical pattern of conglomerate silicosis. Gross and microscopic inspection of tissue from cases, the roentgenograms of which seem identical in all respects with Case iv, customarily show evidences of tissue change that is interpreted as diffuse emphysema. The lack of clear-cut functional evidence of obstructive emphysema in Case iv contravenes even more strikingly than does Case iii the conception that dilated and coalesced alveoli, histologically interpreted as emphysema, must of necessity indicate what might be termed physiologic emphysema. In respect to our measurements of respiratory function in Case iv one might conclude that he is unique, which he is not; that there is too little histologic emphysema to reflect its presence in the physiologic measurements, which seems unlikely; or that the term emphysema as used by the histologist need not always imply those alterations of function that the clinician customarily associates with diffuse obstructive emphysema. Supporting evidence for the divergence between the histologic and functional concept of emphysema was dramatically demonstrated in a reverse manner by Baldwin et al.²⁰ They report a case with a high residual air, very low maximum breathing capacity and impaired lung rinsing for a known period of nine years, which at autopsy showed relatively mild histologic evidences of emphysema.

Case v did show classical functional evidences of emphysema except for the fact that there was a normal terminal alveolar nitrogen. The roentgenogram of this case (Fig. 5) indicates a more widespread involvement of the lung by the

conglomerate process than is seen in Case iv. (Fig. 4.) This suggests that perhaps the explanation for the physiologic difference between these two cases is simply one of extent and duration of the fibrosis. It is equally possible, however, that the distribution of the fibrosis may be different in these two cases.

Assuming that in Case v there is extensive fibrosis of the type commonly observed in conglomerate silicosis, in what way has it influenced respiratory function? The fibrosis cannot be shown to have limited the ability of the lung to be expanded. As indicated by the high residual air and the findings on fluoroscopy, something has limited the ability of the lung to be compressed by the most forceful expiratory effort possible, and has also impaired the speed with which the lung can be emptied. The mere mass of the fibrosis should not impair emptying and there is no evidence, either demonstrable or presumptive, that the lungs are encased in a limiting membrane. The possibility exists that a mechanical obstruction to rib motion or that lengthening of the expiratory muscle fibers so that in their contracted state they are longer than they should be, may contribute to this patient's inability to empty the lungs to a normal degree. This concept appears untenable in view of the studies by Lynn and Wright²¹ which show that in emphysema the intrathoracic pressure is highly positive throughout expiration and does not drop until the succeeding inspiration is initiated. Since we presume the existence of histologic emphysema which connotes fracture of the elastic tissue of the lung, it might be thought that the associated loss of force previously furnished by elastic tissue recoil has impaired the mechanics of expiration. That delayed and limited emptying can be explained solely on that basis is improbable. If the muscular forces of expiration actually exceed or are equal to those of inspiration²² and the emphysematous lung can be distended by the inspiratory muscles, there should also be sufficient force available from the expiratory muscles to deflate the lung without the aid of elastic recoil. The most likely explanation for the high residual air of this case is that the air is trapped behind obstructions in the bronchi, airways that are partially obstructed during inspiration becoming completely obstructed during expiration. This concept fits well with the wheeze customarily heard in emphysema, the low maximum breathing capacity, the high residual air, the

augmentation of maximum breathing capacity and reduction in residual air brought about by bronchodilator drugs and the alterations of intralveolar and intra-esophageal pressures²¹ that have been recorded in classical obstructive emphysema. Whereas loss of elasticity might account for the increased functional residual air commonly observed in emphysema, it will not satisfactorily account for the high residual air.

Is there any evidence that fibrosis causes either the histologic or the physiologic emphysema? The customary explanation for histologic emphysema seen in massive fibrosis, as for example in conglomerate silicosis or extensive fibrocaseous tuberculosis, is that as the fibrosis retracts it pulls on and overdistends the intervening alveoli, ultimately causing rupture of the septa and coalescence of the air sacs. This may be the proper explanation but will it account for the physiologic evidences of bronchial narrowing and obstruction? Such a mechanism would seem more likely to cause simple overdistention in the same way that chronic atelectasis or resection of normal lung tissue do and, from a purely theoretic point of view, this type of overdistention should cause dilatation rather than narrowing of the airways. It should be noted that Case iv simulates the simple overdistended lung in that there is a sub-maximal breathing capacity but no absolute increase of residual air and that, as shown in Table III, a normal work capacity as measured by maximum oxygen uptake is retained. In Case v there is strong evidence of airway obstruction and the histology of the lung in conglomerate silicosis does not supply a definite anatomic explanation for this fact. Peribronchial fibrosis can be discovered but the bronchial passages remain patent and the fibrosis is not particularly prominent nor is it so widespread as one would anticipate it should be in order to cause diffuse obstructive emphysema. Specimens prepared for the specific purpose and more painstaking search for the specific changes might disclose peribronchial lesions such as those described by Amberson and Spain.²³ Even such peribronchial fibrosis would not explain why in life the airways can become entirely closed off during expiration or why the obstruction varies with the application of bronchodilator drugs. One cannot escape consideration of the possibility that fibrosis *per se* has little or nothing to do with the functional abnormalities observed in Case v or in similar

cases. Lymphocytic infiltration of the submucosa of the small bronchi is commonly seen in conglomerate silicosis. Perhaps this finding presages during life a swollen bronchial lining covered with exudate, which combined with smooth muscle contraction might bring about the narrowing of the bronchial lumen needed to explain the altered respiratory function. Death and fixation of tissue may disguise or destroy the evidences we seek.

One additional mechanism that might cause the bronchial narrowing merits mention, if for no other reason than that it will bring us back to a consideration of lung elasticity. In the normal lung those airways that are not supported by cartilage are prevented from collapsing by the lung parenchyma, which is held in a distended state by its attachments to the parietics of the thorax. In effect, the airways are held open by innumerable guy wires amongst which are the elastic tissue strands. Rupture of these elastic strands might conceivably permit lengthening and fracture of the inelastic supports and consequent gradual collapse of the small unsupported airways, so that they open only during inspiration. If this highly speculative mechanism were actually existent, the difference between Case iv and Case v may be only a matter of the extent and duration of the overdistention of the lung. If, as Longacre²⁴ has predicted from animal experiments, the chronically overdistended lung undergoes rupture and coalescence of alveoli, one might anticipate that Case iv will some day have functional as well as anatomic emphysema.

Case vi is that of a fifty-one year old white male who has had pulmonary tuberculosis for twenty-seven years. He was extremely dyspneic on exertion. The roentgenogram taken at the time of our studies is shown in Figure 6. The marked distortion of the thorax, mediastinum and lungs is typical of extensive fibrocaseous tuberculosis. As shown in Table I the total volume was slightly smaller and the residual air much larger than predicted. The maximum breathing capacity was greatly reduced but did increase slightly after the inhalation of a bronchodilator. Although there was little abnormality of the arterial blood gases at rest, during mild exercise arterial hypoxia and the retention of CO₂ became marked. The marked retention of CO₂ during exercise is almost certainly caused by poor ventilation of the alveoli. The almost normal terminal alveolar nitrogen (Table I)

suggests that the distribution and mixing of gases at rest is but slightly impaired and fits well with the resting arterial blood. During exercise, as seen in Table III, the tidal air remained small and minute ventilation was not increased in proportion to oxygen uptake as indicated by the low O_2V . This pattern of breathing almost certainly ventilated the alveoli poorly and most likely accounts for the strikingly underventilated arterial blood during exercise. The maximum breathing capacity in this case was so low that intolerable breathing developed during the fourth minute on the level at 1.5 miles per hour. The extremely small maximum O_2 uptake is indicative of the severe incapacity caused by obstructive emphysema. It is remarkable that such marked blood changes occurred during this mild degree of effort. In the presence of such a limited ability to breathe one cannot determine whether or not the respiratory center is being driven abnormally by measuring the O_2V because breathing cannot be sufficiently augmented to portray the intensity of stimulation that may be emanating from the respiratory center. The sensation of dyspnea was most intense in this patient. This case is presented primarily to demonstrate the severe degree of physiologic emphysema that can develop as a complication of extensive fibrosis.

In summary, Cases IV, V and VI are examples of extensive conglomerate fibrosis distributed throughout both lungs. The histologic alterations can be presumed to conform with those of similar cases that have been autopsied and can thus be expected to exemplify diffuse histologic emphysema of a severity that roughly parallels the numerical order of these cases. That alterations of respiratory function customarily observed in diffuse obstructive emphysema may or may not parallel the histologic emphysema is suggested by these three cases. That the pattern of roentgenogram change exemplified by these cases may or may not be associated with severe physiologic disability is also demonstrated.

Case VII is a thirty-one year old white male who at the time of our studies had two thin-walled tuberculous cavities in the right lung and whose sputum contained tubercle bacilli. Roentgenograms of the chest shown in Figure 7 reveal two thin-walled cavities, marked distortion of the right pulmonary hilum and a density merging with the lung which is located along the right border of the superior mediastinum.

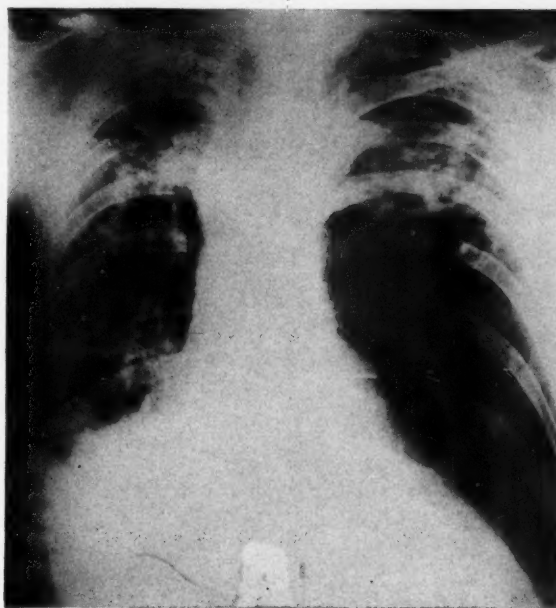


FIG. 6. Case VI. Roentgenogram of chest; full inspiration.

He had a persistent wheeze, especially loud over the right side of his chest, and breath sounds were almost inaudible over most of the right hemithorax. The roentgenogram at full expiration showed that the right lung failed to empty properly and the mediastinum structures shifted to the left during forced expiration. This phenomenon was even more striking when observed with the fluoroscope. Bronchoscopy disclosed no abnormality other than reddening of the mucosa about the right upper lobe orifice. When the right hemithorax was opened surgically, a portion of the upper lobe was seen to be atelectatic. The right lung was removed. Gross examination of the lung revealed the two cavities and the previously mentioned atelectasis of a paramediastinal segment. The branch bronchus to the atelectatic segment was completely occluded. The larger bronchi appeared normal but at or just beyond the secondary branches of most of the lobar bronchi there was an abrupt marked constriction to a pinpoint lumen. The walls of these bronchi were thickened, being 2 to 3 mm. in width. The upper lobe contained a large amount of fibrous tissue, the parenchyma of the middle and lower lobes was pale and dry, the alveoli being slightly larger than normal. Microscopic examination of the smaller bronchi showed that they were surrounded by dense fibrous tissue and distorted so that their cartilages were arranged at an angle to the lumen. Many small tubercles were seen in and about the scar

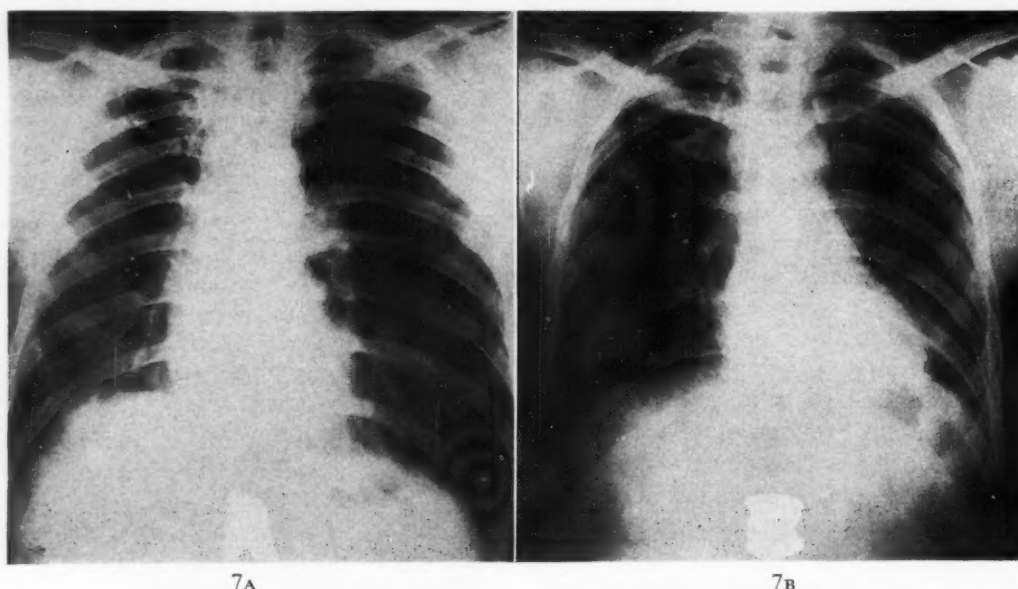


FIG. 7. Case VII. Roentgenograms of chest; A, full inspiration; B, full expiration.

tissue. There were dense lymphoid infiltrations and also frequent tubercles in the submucosa of all bronchi including the main bronchus.

As shown in Table I, the only abnormality of the pulmonary volumina was a slightly high residual air. Apparently, although the right lung did not empty normally, it pushed the mediastinum over and compressed the left lung to an unusual degree. In this way the high residual air of the right lung was masked. The effectiveness with which the lung was rinsed was markedly interfered with as shown by the high terminal alveolar nitrogen, presumably all of the abnormality being in the right lung. The maximum breathing capacity was pathologically low but was surprisingly high in view of the fact that virtually all of the air that was respired came from the left lung. That the right lung did very little breathing and even less of the blood gas exchange is shown in the bronchspirometric measurements of Table IV. The vital capacity tracing showed marked trapping of air in the right lung and could not be measured. The sparse blood gas data shown in Table II indicate subnormal oxygenation of the arterial hemoglobin. Assuming that 50 per cent of the right ventricular output would perfuse the almost non-functioning lung and also assuming a mixed venous blood oxygen during exercise of approximately 7 vol. per cent, one can calculate that under those circumstances the arterial blood should have been only approximately 70 per cent saturated whereas it was actually

found to be 89 per cent. This degree of arterial hemoglobin oxygenation is about what one would expect if 10 per cent of the right ventricular output flowed through the right lung during exercise. Although in Case VII not all of the pulmonary artery blood was shunted away from the poorly ventilated right lung, the major portion of it was. During exercise this patient, as shown in Table III, overventilated. In this instance the arterial hypoxia or perhaps something associated with changes induced by prolonged bed rest may have overdriven the respiratory center. It is equally possible, however, that abnormal reflexes arising in the right lung might also have influenced the breathing pattern. The connection between the alterations of respiratory function and the fibrosis plus inflammation of the bronchial wall and lining is too obvious to require further comment. In summary, this case exemplifies the physiologic alterations that develop by reason of diffuse bronchial obstruction secondary to bronchial fibrosis and inflammation.

Case VIII is a fifty-eight year old white male who died nine months after our study, the diagnosis of pulmonary granulomatosis of beryllium workers being substantiated at autopsy. The details of this case are published elsewhere²⁵ and only the pertinent data will be mentioned here. The roentgenogram shown in Figure 8 is characterized by a fine diffuse granular or stippled appearance throughout every visible portion of the lungs. At autopsy the pleura was

noted to be thickened over the upper lobes but normal over the lower lobes. The lungs were firm and on section appeared to contain more than the normal amount of tissue. The alveoli were described as being fewer in number and coarse. There was a laminated firm thrombus on the wall of the left main pulmonary artery, without occlusion; the distal vessels of the pulmonary artery contained blood. Microscopically, all sections of the lung exhibited "a diffuse, granulomatous inflammation characterized by scattered, stellate lesions which are localized in the alveolar walls and which distort and often obliterate the adjacent alveolar spaces. In addition, the alveolar walls are generally thickened, and the alveolar spaces frequently contain loosely scattered macrophages. The spaces are unusually disproportional and irregular in size. Many are greatly dilated and give anatomical evidence of emphysema."

The histological appearance of the lung was described as follows: "Some of the focal lesions exhibit mild cellular degeneration, while others reveal an appreciable development of loosely woven strands of connective tissue. The latter is most prominent as thin collars about the central foci of large mononuclear cells. An occasional lesion reveals considerable fibrosis and hyalinization. Such lesions are interpreted as the most mature reaction. The arrangement of the fibrosis and hyaline is unlike that which characterizes the reaction to free crystalline silica. The arteries and arterioles embedded in the granulomatous reaction are thick-walled and their lumens appear narrowed. The larger vascular channels of the capillary system are often distended with blood and sometimes project into the alveolar spaces. This is suggestive of passive congestion; however, edematous precipitate is conspicuous by its absence. The smaller capillary systems within the alveolar walls are difficult to identify. Although some small microscopic channels are detected, many walls appear avascular. This observation is subject to criticism since injection studies of the vascular channels were not carried out in this case."

As shown in Table I, there was a marked limitation of the size to which the lungs could be voluntarily expanded. There was no interference with the emptying of the lungs or the rinsing either, as was shown by the normal residual air and terminal alveolar nitrogen.

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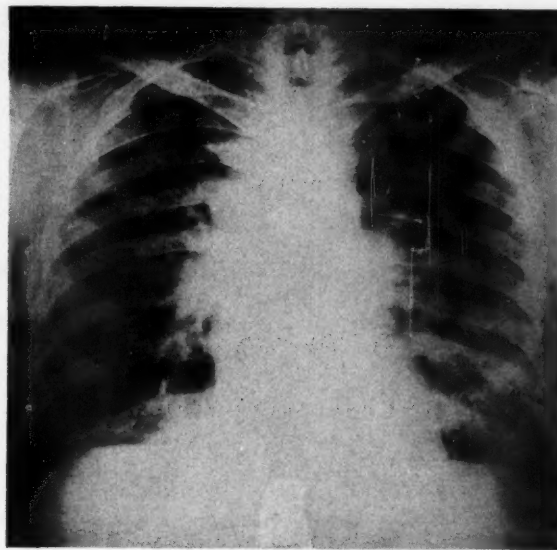


FIG. 8. Case VIII. Roentgenogram of chest; full inspiration.

The maximum breathing capacity was entirely normal, rapid breathing compensating for the short stroke volume. The lungs behaved as though they could be easily stretched to a certain size but could be made no larger regardless of the force used. The arterial blood, Table II, exhibited severe arterial hypoxia during exercise and there was a markedly increased difference between the pO_2 of the arterial blood and alveolar air both at rest and during exercise. In normal persons the pCO_2 and CO_2 content of arterial blood and of the alveolar air drop during exercise. In this patient the alveolar pCO_2 (Henderson trap sample) dropped to 25 mm. Hg but the arterial pCO_2 actually rose and the CO_2 content of the blood dropped only slightly. The low terminal alveolar nitrogen (Table I) and the Henderson trap alveolar pCO_2 during exercise suggest that the lungs were rinsed well and that there was no significant abnormal mixing or distribution of the inhaled air. In view of these facts one is forced to conclude that the tissues supporting the vascular bed constituted an abnormal barrier not only to the passage of oxygen but perhaps to carbon dioxide as well. The histologic alterations afford such an obvious explanation for this abnormal barrier to gas diffusion as to require little further comment. Virtually all of the alveolar septa are abnormally thickened and the masses of granulomatous tissue are very vascular in places. The reason why the hypoxia was not prevented or minimized in this instance by shunting of the flow of blood away from the diseased lung tissue

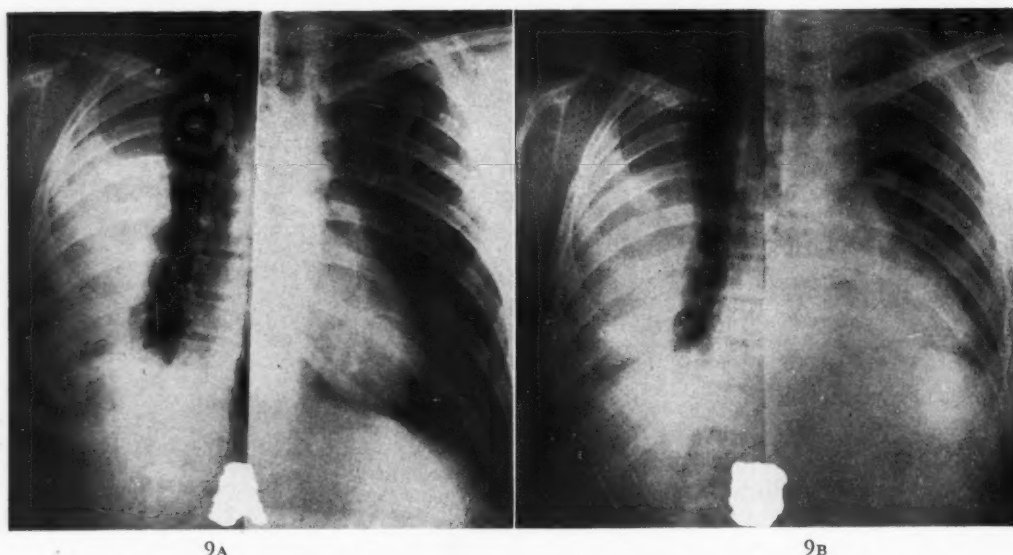


FIG. 9. Case IX. Roentgenograms of chest; A, full inspiration; B, full expiration.

is obvious; there simply was no normal lung tissue into which the blood could be diverted.

The responses to exercise shown in Table III are about as one would anticipate. The overbreathing was so marked that 55 per cent of the maximum breathing power was being used during a walk at 2.5 miles per hour on the level. In order to achieve this high level of ventilation with the restricted stroke volume available, the rate of breathing was markedly elevated. This is in striking contrast to the patient with obstructive emphysema (Case VI) who because of bronchial obstruction could not accelerate air flow and hence could not properly increase his respiratory rate. In Case VIII dyspnea was due to overbreathing and in Case VI dyspnea was due to loss of breathing power. In some cases of pulmonary granulomatosis obstructive emphysema develops as a complicating factor. The marked further crippling effect of this complication was demonstrated in a case reported by Wright et al.²⁶ The overbreathing which was so characteristic of Case VIII was undoubtedly caused to some extent by the arterial hypoxia and hypercapnia but that this was not necessarily the sole cause is evidenced by the fact that in this type of case breathing pure oxygen during exercise does not restore a completely normal respiratory pattern, some overbreathing persisting. Since no blood gas data under this circumstance are available, it is impossible to be certain that the arterial oxygen was raised to normal by breathing pure oxygen. The probability is that stimuli arising from the relatively rigid and undistensi-

ble lung played a role in the overbreathing. The fact that in Case VIII, during the basal state, the lowest minute ventilation observed was 12.5 L. per minute and the respiratory rate was 26 per minute while, at the same time, the arterial blood gases were virtually normal, lends support to this contention. In this type of diffuse fibrosis the functional alterations appear to be adequately explained on the basis of the abnormal histology noted. In summary, this case exemplifies the effect on respiratory function of proliferation of the connective tissue supporting the pulmonary vascular bed distributed throughout all of both lungs.

Case IX is a twenty-two year old white male who, following a stab wound of the right hemithorax, developed a hemopneumothorax which subsequently became empyematous; forty-eight days after the injury he was treated by decortication. This case has been reported elsewhere.²⁷ The roentgenograms at the time of our study, shown in Figure 9, demonstrate an opacity over most of the right hemithorax. The ribs and diaphragm on the right show no change during expiration whereas the left ribs and diaphragm show normal motion and the left lung appears to empty in a normal fashion. Measurements of pulmonary function before (IXa) and after (IXb) decortication of the right lung are shown in the tables. Respiratory function seemed to be almost within normal limits after decortication and one can therefore consider the post-decortication studies to be a control for those done prior to the decortication. Prior to decortication there was

a marked reduction in the total volume of the lung and in the maximum breathing capacity. Bronchspirometry (Table IV) demonstrated that the right lung participated to a considerable extent in quiet breathing but that oxygen uptake from the right lung was low as compared to the quiet ventilation and the vital capacity was more restricted than was the quiet ventilation. In these two respects Case IX is identical with Case I and the same comments regarding blood flow through the injured lung apply in Case IX as in Case I. The explanation for the disproportion between ventilation and circulation in Case IX cannot, however, be the same as it was in Case I since in Case IX there was limitation of chest wall motion and no overdistended lung tissue. In Case I the alveolar volume of the overdistended left lung was enlarged without a commensurate increase in its vascular bed and motion of the thorax remained normal. It may be that in Case IX the right lung and its capillary bed were collapsed so that the vascular bed resistance was elevated and that during each inspiration, although the alveoli could enlarge and take in air, the lung as a whole was not enlarged enough to lower the peripheral vascular resistance and thus permit a commensurate flow of blood. The blood which did flow through the right lung was properly ventilated as is shown by the sparse data in Table II. The data in Table III show a marked limitation of work capacity prior to decortication, intolerable dyspnea being reached when the oxygen uptake was only 0.650 L. per minute per square meter of body surface. The low maximum breathing capacity was the primary reason for the diminished exercise tolerance but, as indicated by the O_2V , there was also an element of overbreathing. The increase in maximum breathing capacity and reduction of O_2V subsequent to the decortication permitted the same stint of exercise to be performed without any complaint whatever of respiratory discomfort. That decortication reduced the O_2V suggests that impulses arising from the "bound lung" or its parietes before decortication drove the respiratory center in an unusual manner. The serious consequences that attend fibrosis which limits lung motion require little further comment. It is worth while pointing out that in Case VII bronchial obstruction with the added factor of poor lung rinsing produced respiratory abnormalities similar to those of Case IX. If it had not been for the compensatory changes in pulmonary blood distribution the respiratory abnor-

malities of Case VII would almost certainly have been even more severe.

In summary, Case IX exemplifies the effect on respiratory function of extraparenchymal fibrosis that binds or encases the lung, thus interfering mechanically with motion of the involved parts.

This paper does not represent a complete discussion of the problems stated at the outset. Since the primary effects of pulmonary fibrosis on the pulmonary vascular bed and the lesser circulation are the subject of another paper of this series, this point will not be discussed here. Primary heart disease also influences pulmonary function but will not be discussed other than to mention that the external manifestations of cardiac and of respiratory insufficiency, conditions which may coexist, are in many respects the same and therefore difficult to distinguish. Primary heart disease may cause pulmonary fibrosis²⁸ but the lack of adequate data makes a discussion of the consequent alterations of respiratory function impossible. Certain other rather rare forms of pulmonary fibrosis, such as pulmonary scleroderma for example, have also not been discussed.

CONCLUSIONS

1. Fibrosis, even though extensive, may fail to cause any measurable evidence of altered respiratory function. In this regard the inadequacies of our methods of measurement must be borne in mind.

2. Fibrosis may alter pulmonary function by (1) destroying or replacing tissue; (2) restricting movement of the respiratory apparatus; (3) impeding the flow of air through the bronchial passages; (4) impairing alveolar rinsing by reason of (2) or (3); (5) impeding the passage of oxygen and perhaps carbon dioxide across the barrier that separates the gas from the blood phase of the alveoli and (6) causing abnormal patterns of breathing by reason of stimuli which arise directly from within the tissues of the diseased respiratory apparatus.

Thus all of the situations anticipated by *a priori* considerations are discoverable in actual fact except those which deal with alterations of the diffusion surface and the relationship of volume and speed of blood flow to alveolar size and ventilation. Techniques suitable for studying these latter relationships are as yet not reliable or have not been applied sufficiently to warrant comment.

3. Reduction of maximum breathing ca-

capacity, abnormal patterns of respiration and alterations of the arterial blood gases are the common manifestations of altered respiratory function associated with fibrosis of the respiratory system. In some instances these alterations appear clearly to be a result of the fibrosis but in others the alterations have no apparent or discoverable causal relationship to the fibrosis.

4. There is no specific pattern of fibrosis that invariably is associated with or leads to a specific manifestation of altered respiratory function. This fact helps to explain the poor correlation which exists between the type and severity of the physiologic alteration and the coincident histologic or roentgenographic abnormality.

5. From the standpoint of its influence on pulmonary function, fibrosis is relatively benign unless the physiologic alterations that characterize diffuse obstructive emphysema develop. The exception to this generalization is the relatively uncommon case of fibrosis in which the majority of the alveoli are involved by a thickening of the tissues that support the capillaries of the pulmonary artery.

6. There is evidence suggesting that what might be termed histologic emphysema is not necessarily synonymous with physiologic emphysema.

7. Specific disease of the lungs, for example tuberculosis, Boeck's sarcoid, silicosis or bronchiectasis, may or may not be accompanied by discoverable alterations of respiratory function. It is equally true that identical abnormalities of respiratory function may be associated with or caused by different diseases.²⁹

8. The effectiveness with which pulmonary artery blood is shunted away from diseased and improperly functioning alveoli and channelled through properly functioning ones, thus preventing serious underventilation of the venous blood, is demonstrated by these cases. The importance of this phenomenon has been inadequately appreciated.

SUMMARY

From *a priori* considerations we have made an attempt to predict the manner in which pulmonary fibrosis might alter respiratory function. Confirmation of these predictions has been sought in a study of the alterations of respiratory function that are discoverable in diseased individuals who exemplify the various patterns of fibrosis. Although most of the pre-

dictions were confirmed, no specific pattern of fibrosis was found to be invariably associated with a specific alteration of respiratory function.

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Case Report

Coexisting Acromegaly and Cushing's Syndrome*

Discussion of Hormone Production by the Pituitary Acidophilic Cell

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IN view of the current interest in the adrenal corticotrophic hormone and the physiology of the adrenal and pituitary glands, a discussion of the cellular origin of ACTH and growth hormone based on an unusual case is presented. This case combines the typical findings of acromegaly and Cushing's syndrome and is the first documented case of this combination in the literature.

Acromegaly, first described by Marie in 1886, has been attributed to an increase in growth hormone secreted by the acidophilic cells of the anterior pituitary and is frequently characterized by overgrowth of the bones of the skull and hands, enlargement of the viscera and diabetes. The syndrome of obesity, hirsutism, hypertension, sexual dysfunction, osteoporosis and diabetes, which had previously been attributed to adrenal hyperactivity, was fully described in 1932 by Harvey Cushing¹ who believed it was due to basophilic adenomas of the pituitary. In more recent years it has been realized that Cushing's syndrome may be caused in most cases by primary disorders of the adrenal cortex.

Cushing's syndrome has been associated with adenomas of all three cell types of the pituitary gland. Bland and Goldstein² col-

lected all the cases of patients with Cushing's syndrome who had pituitary tumors up to 1937. The majority had basophilic adenomas but there were three chromophobe, two acidophilic and one non-granular adenomas. Lissner³ reported more fully one of these cases of Cushing's syndrome with a chromophobe adenoma. This patient was treated with hypophysectomy, with temporary improvement but eventual death. The adrenal glands appeared normal by air insufflation studies and the left adrenal was proved normal by operation, but the pituitary showed a chromophobe adenoma. In 1947 Forbes⁴ reported a case of Cushing's syndrome found at autopsy to have carcinoma of the pituitary gland of chromophobe cell type, but there were metastases to the liver which were acidophilic.

Acromegaly and Cushing's syndrome have always appeared as separate entities, but in the literature there are occasional references to cases appearing to combine certain features of both conditions. In Cushing's classic monograph¹ on pituitary basophilism he refers to a case described by Erdheim as a case of acromegaly with a basophilic adenoma as well as an acidophilic tumor. Although details are lacking in this case, it did not appear to exhibit any

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of the characteristics of Cushing's syndrome. Cushing commented in this one case of Erdheim's that acidophilic and basophilic adenomas may exist in acromegaly but there was only one case to illustrate it. In the same monograph a case of Reichman's⁵ in which the patient had a chromophobe adenoma with acidophilic granular elements was interpreted by Cushing to be a case of Cushing's syndrome but by Reichman as a case of acromegaly. Few details of this case were given.

Bickel⁶ in 1945 reported a case of acromegaly with paroxysmal hypertension and virilism. Diabetes was not present. The left adrenal gland was removed and found to be histologically normal but the hypertension was relieved. There were no hormone studies or follow-up examinations reported. Moehlig⁷ reported a case of acromegaly with typical findings except for a blood pressure of 160/100. The patient died in cardiac decompensation and at postmortem there was hyperplasia of both acidophilic and basophilic cells of the pituitary but no tumor was present. The thyroid and parathyroids were enlarged and an adenoma was present in the right adrenal gland. Soulie and de Vericourt⁸ reported a case of a woman with acromegaly, hyperthyroidism, hirsutism and amenorrhea but no diabetes. At operation an acidophilic adenoma was found but no further studies were reported. Flaum and Ralli⁹ reported a case of acromegaly with hirsutism, hypertension, virilism and diabetes. At autopsy normal ovaries and adrenal glands and an acidophilic adenoma were found. Daughaday, Perry and MacBride¹⁰ have reported a case of acromegaly that showed increased adrenal cortical hormone excretion. This interesting case was not clinically suggestive of Cushing's syndrome. A case of pituitary carcinoma with Cushing's syndrome has been reported recently by Davidoff.¹¹

CASE REPORT

A forty-six year old Negro practical nurse was admitted to the Roosevelt Hospital with the chief complaint of diminution of vision and

weakness. The family history did not include diabetes or endocrine disturbances. The patient had been borne in New York City and had lived there all her life. She was married and had five children, one of whom had died in infancy; the other children were living and well. The patient's habits were not unusual and there was no excessive use of tea, coffee, alcohol or tobacco. The only medication was phenobarbital four times a day which she had been taking for her hypertension. Her past health was generally good. She had had no acute or infectious diseases but had been immunized for smallpox in 1947. There was no history of allergies, operations or injuries. Three years before entry she had weighed 210 pounds and at the time of entry she weighed 184 pounds.

The patient had been in good health until nine years before admission following the birth of her youngest child. Thereafter she had but one menstrual period, two years later. Hypertension developed after delivery of her last child but the patient had treatment only during the last four years. The therapy consisted of a low salt diet, decrease in activity and phenobarbital. During the past four years she had occasional palpitation and gradually increasing dyspnea on exertion and slight swelling of the ankles in the late afternoon. She never had any marked symptoms of cardiac decompensation or angina pectoris. She complained of occasional headaches with hot flushes through the day; the headaches were described as "hot rings" around her head and were an annoying type of pain which had occurred occasionally for the previous two or three years. As long as she could remember she had a certain amount of hair on her face but this definitely increased in amount during the past four years. Her shoe size increased from seven to ten and her glove size from six to eight in the same period. She became obese over the last several years but this weight gain was so gradual that it passed unnoticed.

She had gradual increase in neurologic symptoms for four years which were particularly bad for the last four months. These consisted of difficulty in walking, staggering and a feeling of dizziness. She complained of paresthesias in her fingers and inability to tell whether she was holding things in her hands. Generalized weakness also developed and she was unable to perform her accustomed amount of work. In the

last few months she noted slight deafness and diminution of vision.

She was under the care of her family doctor who reported she had diabetes for only two years and until very recently it was so mild that it did not require insulin or special diet. In the last four months she had glycosuria and pruritus vulvae with urinary frequency and was on a special diet. Because of the progression and severity of the diabetes and the discovery of acetone in her urine for the first time, she was referred by the doctor to the hospital.

On entry to the hospital the patient had a normal temperature, pulse and respiration. Blood pressure in the right arm was 250/130 and in the left arm 230/120. The patient was an obese colored woman with a round moon-face, puffy eyelids and large, coarse, spade-like hands and feet. There were pustules on the face and neck and several old scars and sebaceous cysts were present. There were no definite abdominal striae but there were small striae over the buttocks and thighs. There was obesity of the trunk, upper arms and thighs but not of the forearms and legs. The skin was of rather coarse texture. There was an increase in the facial hair with the individual hairs measuring up to 1 cm. in length over the usual male beard distribution. The axillary and pubic hair were normal and there was a female escutcheon. The head presented no gross abnormality. The pupils were normal and examination of the fundi revealed a slightly pale right disc but was otherwise normal. Perimetry showed a complete bitemporal hemianopsia and diminution of the visual acuity (left eye 10/120, right eye 10/30 corrected); examination of the ears, nose and throat revealed no abnormality. The hands and feet were enlarged. The lymph nodes were normal. The breasts were pendulous. The lungs were clear and the heart was slightly enlarged to the left with distant sounds and with soft apical and aortic systolic murmurs. There was regular sinus rhythm. The abdomen was obese but no organs, masses nor tenderness were found. The external genitalia were normal; the clitoris was not enlarged. Neurologic examination was normal except for the perimetry. (Fig. 1A and B.)

Laboratory examination revealed the following: The hemoglobin was 12.8 gm. with a red blood count of 4,200,000 and a white blood count of 8,600 with 66 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes

and 6 per cent monocytes. Urinalysis revealed specific gravity of 1.020, albumin 2 plus, sugar 4 plus and acetone 1 plus. There were numerous red blood cells and occasional white blood cells in the sediment. The albuminuria and microscopic hematuria were consistent findings throughout her illness but the sugar and acetone fluctuated. The sedimentation rate by the Cutler method was 14 mm. in one hour. The blood Kline and Mazzini tests were negative.

The blood urea nitrogen was 11 mg. per cent and the admission blood sugar 261 mg. per cent. The serum sodium was 142 milliequivalents per liter and the serum chloride 98 milliequivalents per liter with a serum potassium of 4.95 milliequivalents per liter. Later, several determinations of potassium averaged about 3.5 milliequivalents per liter. The CO₂ combining power was 70 volumes per cent, the serum phosphorus 2.3 mg. per cent, the serum cholesterol 405 mg. per cent and the serum calcium 11.5 mg. per cent. A urinary concentration test revealed maximum specific gravity of 1.037 and the dilution test, specific gravity of 1.012. The phenolsulfonphthalein excretion was 25 per cent in fifteen minutes and 45 per cent total in two hours.

A spinal tap showed an initial pressure of 205 mm. of water, the dynamics were free, the cell count was negative, as was the Wassermann test, and the colloidal gold curve was 1112332100. The protein was 206 mg. per cent, the sugar 198 mg. per cent and the chloride, expressed as sodium chloride, was 802 mg. per cent.

Fasting blood sugars varied between 200 and 260 mg. per cent, but on 25 units of protamine zinc insulin daily they ranged between 130 and 180 mg. per cent. A glucose tolerance test revealed a fasting level of 256 mg. per cent, 314 at one hour, 365 at two hours and 470 at three hours. The glucose tolerance test with 0.1 unit of insulin per 10 kg. of body weight revealed a fasting level of 210 mg. per cent with a blood level of 594 after thirty minutes, 500 after forty minutes, 450 after fifty minutes, 410 after sixty minutes, 377 at one hour and forty minutes and 399 at two hours.

Two basal metabolic rate determinations were minus 10 and minus 16. An electrocardiogram showed depressed ST segments in leads I and CF6 with inverted T waves in these leads, which was interpreted as consistent with potassium deficiency.

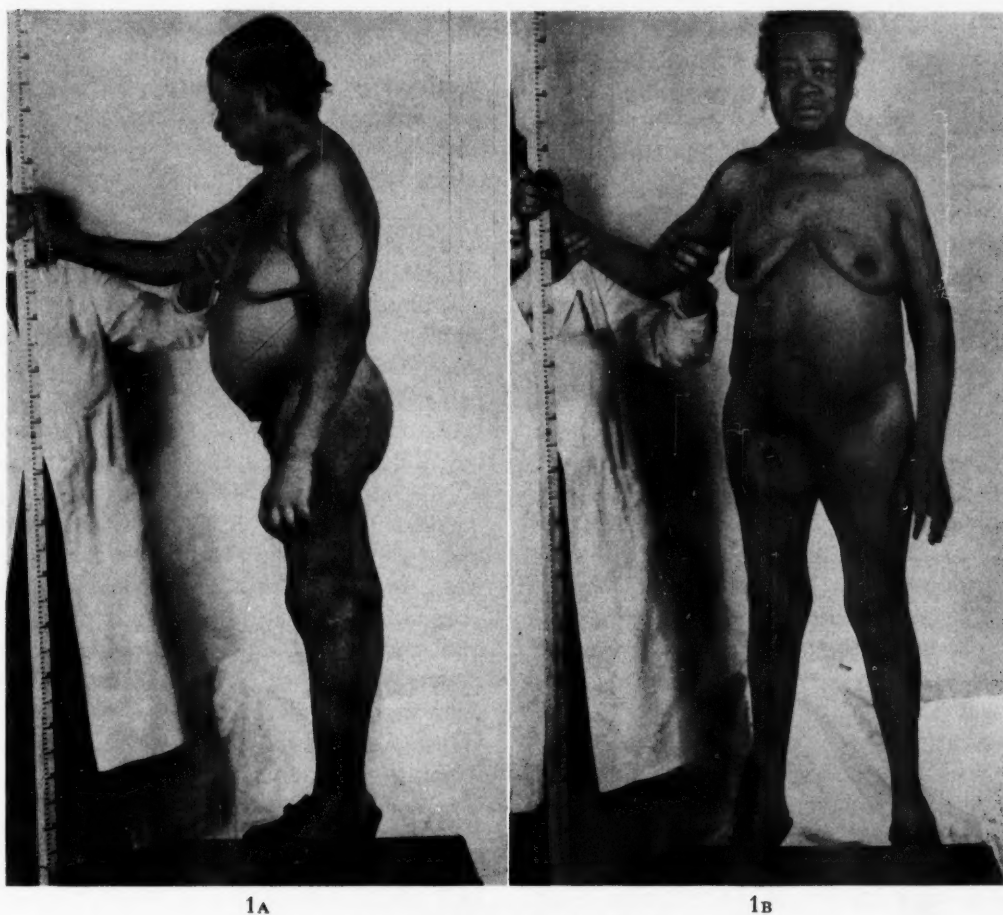


FIG. 1. A and B, appearance of patient before operation.

Roentgenograms of the chest showed a moderate cardiac enlargement with a cardiothoracic ratio of 14.5:25. The cardiac shadow was transverse in type and appeared to have some accentuation of the left ventricular segment. There was slight bilateral congestion of the pulmonary vascular shadows.

Roentgenograms of the skull showed a moderate degree of prognathism and thickening of the cranial bones. The sella turcica was enlarged and had a ballooned appearance. It measured 2.7 cm. in the long diameter. The posterior clinoids and the dorsum sellae were eroded and the anterior clinoids sharpened. The floor of the sella was intact. The sinuses were not enlarged. The films of the hands and feet showed minimal tufting of the terminal phalanges. An intravenous pyelogram showed poor concentration but prompt excretion. Visualization of the calices was unsatisfactory but the dye entered the urinary bladder without difficulty. Air insufflation studies of the perirenal regions were interpreted as ruling out adrenal tumor.

MAY, 1951

Fasting circulating eosinophile counts revealed levels of sixteen, thirteen and seventeen cells per cubic millimeter. After 0.5 mg. of epinephrine there was no significant drop in four hours. Analysis of the urine over a ninety-six-hour collection period revealed the 17-ketosteroid level to be 36.7 mg. per twenty-four hours. The excretion of the formaldehydogenic steroids was 11.1 mg. per twenty-four hours. These values are both abnormally high and conform with those found in many cases of Cushing's syndrome. The follicle-stimulating hormone excretion in the twenty-four-hour urine specimen was negative at 6.5 MU. A bioassay for ACTH in the serum was performed. The serum gave a significant reduction in the adrenal ascorbic acid of hypophysectomized rats, indicating the presence of adrenotropic activity. Ordinarily, only the serum of patients with Addison's disease possesses adrenotropic activity, whereas those with Cushing's syndrome do not.¹²

The benzodioxane test using 2 mg. per kg.

of body weight revealed a slight rise in the blood pressure. A test dose of 5 cc. of tetraethyl ammonium chloride intravenously caused a very slight rise in blood pressure. After oral administration of 0.6 gm. of sodium amytal the blood pressure fell to 160/80.

For preoperative preparation the patient was transferred to Memorial Hospital in order that hormone and metabolic balance studies might be carried out at the same time. These were reported by Eliel and Pearson.¹³ During this time the patient continued to exhibit hypokalemia, hypophosphatemia, hypochloremia and metabolic alkalosis. Analysis of dry fat-free muscle revealed potassium and phosphorus content 20 and 30 per cent below normal, respectively. She was given 6 to 12 gm. of potassium salt per day which raised the serum potassium to 4.3 milliequivalents per liter. The electrocardiogram reverted to normal and the carbon dioxide content and pH of the blood returned to normal levels. During the preoperative period the blood pressure was between 180/110 and 140/96.

A transfrontal craniotomy was performed at the New York Hospital by one of us (B. S. R.). A large pituitary adenoma was exposed and sufficient tumor removed to decompress the optic nerves.

Histologic examination of the tumor sections stained by hematoxylin and eosin revealed sheets of large polygonal cells with round uniformly staining nuclei which varied only slightly in size. Scattered throughout were gland-like acinar spaces. The cells had abundant cytoplasm, approximately half of which took a deep eosinophilic stain. The remainder also took on eosinophilic stain but of paler quality. The cytoplasm showed uniformly fine granules. No basophilic cells were seen.

Postoperatively the patient reacted well and was placed again on potassium salts and insulin medication. Although the wound healed well, on the sixth postoperative day the patient became somewhat lethargic and markedly confused. The following day she was moderately agitated and expressed many poorly organized paranoid delusions. The aberrations in her behavior were compatible with an organic psychotic reaction. Over the next several days her mental state improved and she was again transferred to Memorial Hospital where further postoperative studies were contemplated. Visual field examination showed some improvement in visual acuity but no essential change in the results of perimetry. The patient showed con-

tinuation of her mental abnormalities and was unable to cooperate with the metabolic ward routine. An ACTH determination of the serum was done and found to be normal, but the formaldehydogenic steroid excretion was decreased and the 17-ketosteroids were unchanged.

Two weeks later frequent convulsions and fever developed and the patient was transferred to the New York Hospital. An exploratory craniotomy disclosed a subdural empyema which was drained. Death occurred four days later (December 26, 1949) and an autopsy was performed.

Postmortem examination revealed the following: The body presented a bizarre appearance of disproportion. The trunk was obese and barrel-like with a very protuberant abdomen while the legs were thin. The hands and feet were unusually large and there was moderate prognathism. The face was rather moon-shaped and there was marked hirsutism, especially about the mouth. The skin was moderately deep brown and there were innumerable large violaceous subcutaneous nodules over the chest which, when incised, were cystic and contained a yellow pultaceous material.

Except for the multiple sebaceous cysts, some of which were infected, the subcutaneous tissues and muscles were normal. The abdominal panniculus averaged 3.5 cm. in diameter and the muscles were well developed and somewhat pale. There was no appreciable amount of free fluid in the peritoneal cavities and the surfaces were smooth. The domes of the diaphragm rose to the fourth interspace on the right and the fifth rib on the left. There was no trace of the thymus; the relationship to the mediastinal structure was normal. There was no fluid in the pleural cavities and the surfaces appeared normal except for a few thin apical adhesions. There was only about 10 cc. of clear yellow fluid in the pericardial cavity and the surface appeared normal.

The heart weighed 350 gm. and the left ventricular wall measured 19 mm. in thickness at the base with the right wall measuring 4 mm. The valve circumferences were within normal limits. No lesions were found in the myocardium over the endocardial surfaces. The coronary vessels showed only slight arteriosclerosis. The great vessels were unremarkable except for slight atherosclerosis of the abdominal aorta.

The thyroid was medium sized, firm and uniform in consistency. The pharynx and trachea were normal. The lungs weighed 940

gm. and appeared normal on gross section. There was very little fluid and no areas of consolidation. The hilar nodes were slightly enlarged. The spleen weighed 60 gm. and was unremarkable. The liver weighed 1,800 gm. and was very flabby and yellow-brown. The gallbladder and biliary structures were normal. The gastrointestinal tract was normal. The substance of the pancreas was mottled with large irregular areas of hemorrhage. No obstruction could be demonstrated in the duct system.

The adrenals weighed 26 gm. together and were much enlarged in proportion to the other organs. They showed small, red nodular areas ranging up to 4 mm. in diameter scattered over the cortical surface. The kidneys weighed 350 gm. and presented a rather fine granular cortical substance from which the capsule stripped with ease. On cross section the architecture was well preserved and the ureters and bladder were normal. The uterus was small, firm and not nodular. The ovaries were normal except for a few small serous cysts. The lymph nodes were normal. The bones and joints appeared normal to external examination. There was marked osteoporosis and the vertebral bodies could be cut easily with a knife. The vertebral marrow was red and fairly firm.

There was a large soft tumor mass in the sella turcica which was enlarged to about 3 cm. in diameter. This pituitary tumor was bathed in purulent material. At the left anterolateral extent of the sella turcica just medial to the foramen rotundum there was a 6-mm. erosion from the sphenoid sinus into the base of the cranial cavity from which necrotic mucous membrane and mucoid material could be readily extracted. The border of the erosion was fairly smooth and quite firm. Purulent exudate extended from this area beneath the dura to the right frontal region where surgical drainage was effected.

The brain weighed 1,060 gm. The vessels at the base of the brain showed slight sclerosis and there was some subarachnoid hemorrhage over the pons and the anterior spaces of the cerebellum and in the intrapeduncular space. The optic chiasm was markedly flattened and thinned out. A fragment of what appeared to be tumor tissue was just lateral to the right carotid artery. The cerebral veins were congested with several areas of subarachnoid hemorrhage over both cerebral hemispheres. There was some thickening of the arachnoid over the hemispheres. Cortical atrophy was present over the frontal

parietal regions. The falx cerebrae between the frontal lobes revealed softening and had a peculiar mottled appearance. The anterior horns were normal in size and the third ventricle was normal except at its extreme anterior portion where it was ballooned out beneath the thin optic chiasm. Sections through the frontal lobe showed hemorrhage through the frontal pole on the right.

On microscopic examination the myocardium was essentially normal. Section of the right coronary artery showed large atheromatous plaques into which hemorrhage had occurred and had partially occluded the lumen. In the lungs the alveolar walls were thin and the spaces for the most part were devoid of fluid or cells. However, in a few areas there were considerable numbers of granulocytes filling the alveoli together with a small amount of fibrin. In the liver there was extensive fatty metamorphosis involving the majority of the hepatic cells and there was moderate congestion of the central veins in some areas. The spleen sections were normal. A great deal of extravasated blood and edema was present throughout the inner tissue of the pancreas which extended into the lobules around the acini. In addition, in some areas there were large areas of polymorphonuclear leukocytes indicating antemortem reaction. Sections of the kidney showed that the glomeruli were generally unaltered although a few showed fibrosis and hyalinization. The small blood vessels showed considerable hyalin thickening of the walls with compression of the lumen.

In the adrenals there was proportional thickening of the entire wall of the adrenal cortex and medulla. The small red nodules noted grossly on the cortical surface were found to be small nodular areas of hyperplasia. (Fig. 2.)

Multiple sections of the pituitary showed it to be largely replaced by tumor tissue made up of irregular ovoid cells having moderately abundant granular acidophilic cytoplasm and dark round nuclei. There were a few islands of large cells with sparse faint granulation of the cytoplasm which stained with eosin. The Mallory-Azan method revealed these cells to be basophiles. Some of them showed changes very closely resembling those described by Crooke in Cushing's syndrome. Chromophobes could also be identified.* (Fig. 3.)

The parathyroid showed a good deal of

* We are indebted to Dr. A. A. Koneff, Berkeley, California, for this interpretation.

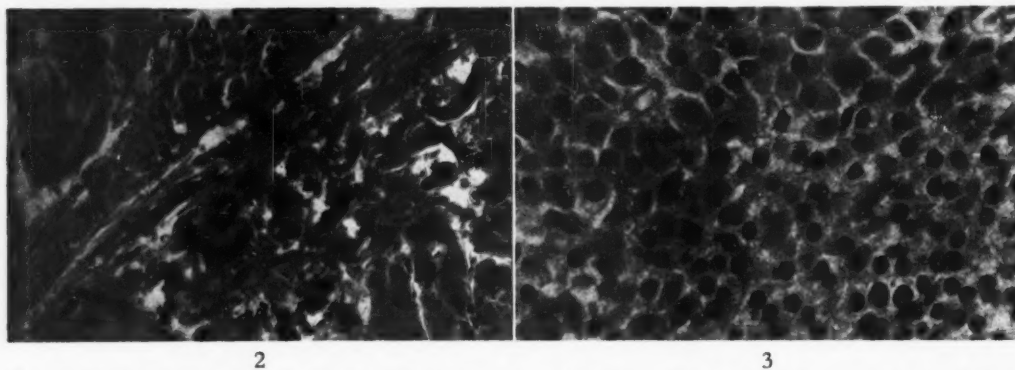


FIG. 2. Photomicrograph of the adrenal cortex; note the hyperplastic adrenal cortex in the lower portion and the encapsulated adenoma in the upper portion of the section; 300 \times .

FIG. 3. Photomicrograph of the acidophilic adenoma of the pituitary; 900 \times .

stromal fat with the normal proportion of chief and clear cells. The gland appeared somewhat atrophic. The epithelium of the thyroid was definitely flatter than normal and appeared atrophic. The architecture was generally unaltered.

The myometrium appeared normal. The endometrial glands were in the resting stage and showed no other noteworthy feature. The ovary contained numerous corpora albicantia and a few serous cysts.

Examination of the skin showed that the epidermis was thin and atrophic, but there were no other changes. The breasts were unremarkable.

The bony trabeculae were very thin and atrophic and the marrow was relatively decreased in cellularity.

COMMENTS

This case of coexisting Cushing's syndrome and acromegaly with an acidophilic adenoma of the pituitary, adrenal hyperplasia and an elevated level of ACTH in the blood is not only unique but also affords evidence of the cellular origin of ACTH.

Hypersecretion of the acidophilic cells of the pituitary produces various manifestations of acromegaly and the pathology of this disease is usually predictable. Most patients with acromegaly have been found to have acidophilic hyperplasia. However, occasionally no lesions can be found and it must be postulated that there is physiologic hyperactivity. To explain the occurrence of adenomas of the adrenals, thyroid, parathyroids and pancreas which frequently occur in acromegaly it had been suggested that the acidophilic cells of the pituitary may produce other tropic hormones besides

the growth hormone. Albright^{14,15} has championed this theory and has shown evidence of increased excretion of urinary steroids in acromegalics.

Concerning the sequence of events in Cushing's syndrome there are two schools

TABLE I
PRODUCTION OF ANTERIOR PITUITARY HORMONES
BY CHROMOPHILIC CELLS

Acidophilic Cells	Basophilic Cells
Adrenocorticotrophic hormone	Follicle-stimulating hormone
Thyrotrophic hormone	
Diabetogenic hormone	
Growth hormone	
Lactogenic (prolactin, luteotropic) hormone	
Luteinizing hormone	

of thought. Followers of Cushing believe that hypersecretion of the basophilic cells of the pituitary is the initial pathologic condition and that the adrenal cortical lesions often seen are secondary to this. Other investigators¹⁵ hold that the adrenal cortex is the primary seat of the disease and that hypersecretion of this gland produces the complete clinical picture. The Crooke cell changes and the basophilic tumors are thought to be secondary or incidental to the adrenal pathologic condition.

Table I, adapted from Albright,¹⁴ presents his theory of the hormone production of the acidophilic and basophilic cells. Some aspects of this theory are advanced on a hypothetical basis. It will be noted that all of the active principles of the anterior pituitary except follicle-stimulating hormone

(FSH) are produced by the acidophilic cells. FSH is the only hormone produced by the basophilic cells. Hyperactivity by the acidophilic cell would then be expected to produce greater amounts of all hormones except FSH. If this were the case, one might expect that acromegaly and Cushing's syndrome could occur together. Instead, if it is postulated that ACTH and FSH arise from the basophilic cells and the other hormones from the acidophilic cells, hypersecretion of the basophilic cell might cause Cushing's syndrome but not acromegaly. According to this latter theory an acidophilic adenoma would be unable to produce Cushing's syndrome and a normal or hypoactive adrenal would be expected. If ACTH arises from both the acidophilic and basophilic cells, one would expect overproduction of either cell type to cause Cushing's syndrome.

The origin of this patient's acromegaly was almost certainly due to the increased production of growth hormone by the acidophilic adenoma. In her case there are two possibilities for the origin of Cushing's syndrome. The first is that she had primary hyperplasia or adenomas of the adrenal gland in addition to and coincidental with adenoma of the pituitary. The other is that possibly the pituitary was producing greatly increased amounts of ACTH as well as growth hormone. In either case it would be expected that adenomas or hyperplasia of the adrenal glands would exist, as was proved at autopsy. Differentiation between these two possibilities might therefore depend upon the level of ACTH circulating in the blood. If adrenal hyperplasia were the primary lesion, a normal or, more likely, a depressed level of ACTH would be expected in accordance with the general principle that the production of a tropic hormone is diminished by the presence of an increased amount of hormone produced by that particular end-organ. However, if the pituitary were producing adrenal hyperplasia by secreting adrenal corticotrophic hormone, one would expect an increased amount of this hormone to be present. In

an attempt to settle this question a sample of the patient's serum was analyzed and found to contain demonstrable amounts of ACTH. This finding also would appear to eliminate the possibility that adrenal hyperplasia and adenomas were caused by the growth hormone. Since both basophiles and acidophiles were present in this pituitary, it is possible that the acidophilic tumor produced growth hormone while the basophiles were independently hypersecreting ACTH. However, it seems more reasonable to us to assume that the obviously overactive acidophiles were producing both hormones.

Keeping in mind that the basophilic adenomas are usually small and difficult to find and that the staining characteristics of the pituitary cells may lead to confusion in differentiation of cell types, we could find only a few basophilic cells in sections of the surgical specimen. The fact that ACTH production diminished after partial removal of the acidophilic tumor suggests that these cells were producing this hormone. Physiologic evidence of diminished activity of the basophilic cells is further suggested by the low level of FSH in this patient. If this woman at the age of forty-six was in the menopause, one would expect to find increased amounts of FSH; none was found, suggesting a great reduction in the function of the basophilic cells. This established case of Cushing's syndrome with increased amounts of ACTH in the blood and an acidophilic adenoma in the pituitary leads to the following speculations:

Although acidophilic adenomas occupying the entire pituitary gland have sometimes been found, basophilic adenomas usually exist together with acidophilic cells in the pituitary. In "pituitary basophilism" hormone production by the pituitary might therefore come from either cell type. In this case the absence of basophilic cells would indicate that ACTH was produced by the acidophilic cell. This possibility suggests that "pituitary basophilism" may originate from hyperplasia or hypersecretion of the acidophilic cells and that the commonly found basophilic adenoma may be second-

ary. Whether the resulting syndrome is a direct effect or mediated through the adrenals or by some other mechanism cannot yet be stated. In our case both Cushing's syndrome and acromegaly appear to be related to an acidophilic adenoma of the pituitary.

The decision to treat this patient with partial hypophysectomy rather than with irradiation was made because of the local pressure phenomena of the tumor on the optic nerves and to avoid the danger of postirradiation edema. The cause of death was subdural empyema which occurred following an erosion through bone from a chronically infected sphenoid sinus into the cranial cavity. This erosion took place on the left side of the sella turcica away from the area of operation. Although resistance to infection is notoriously poor in Cushing's syndrome, a subdural empyema from such an erosion is very rare.¹⁶

SUMMARY

1. A case of coexisting acromegaly and Cushing's syndrome with an acidophilic adenoma of the hypophysis and hyperplasia and adenomas of the adrenal glands is presented.

2. Demonstration of increased amounts of ACTH in the blood indicated that the acidophilic adenoma of the pituitary was probably the cause of Cushing's syndrome as well as the cause of the acromegaly.

3. The patient was treated with partial hypophysectomy. The immediate cause of death was a subdural empyema due to erosion of an infected sphenoid sinus into the cranial cavity.

4. A survey of the literature reveals that a variety of pituitary tumors, other than basophilic adenomas, have been described with Cushing's syndrome. There have been a few cases of acromegaly with some features suggestive of Cushing's syndrome.

5. This case indicated that ACTH may be produced by the acidophilic cells of the pituitary and that hyperadrenalism and acromegaly may be the result of such an acidophilic adenoma.

Acknowledgment: We wish to express our appreciation to Dr. Konrad Dobriner of the Memorial Hospital in New York City for his cooperation and permission to publish the result of his analyses of the adrenal hormones. We also wish to thank Dr. A. Albert of the Mayo Clinic for the determination of the blood ACTH and the Pathology Department of the New York Hospital and the Cornell Medical College for the use of the postmortem protocol.

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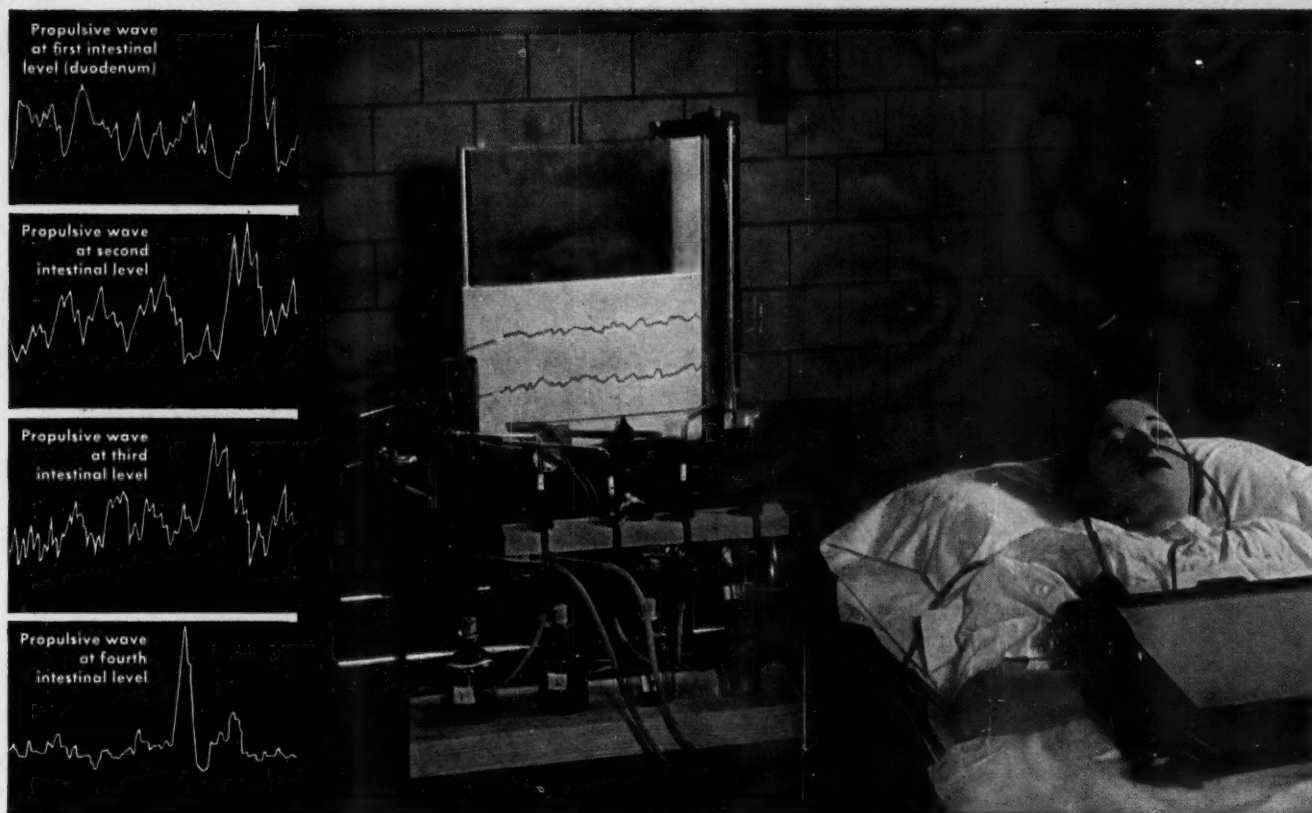
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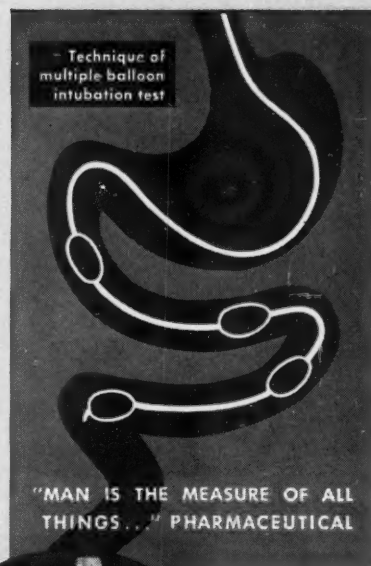
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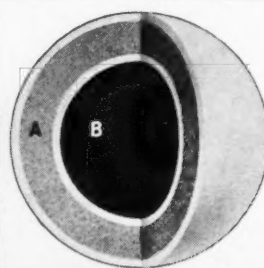
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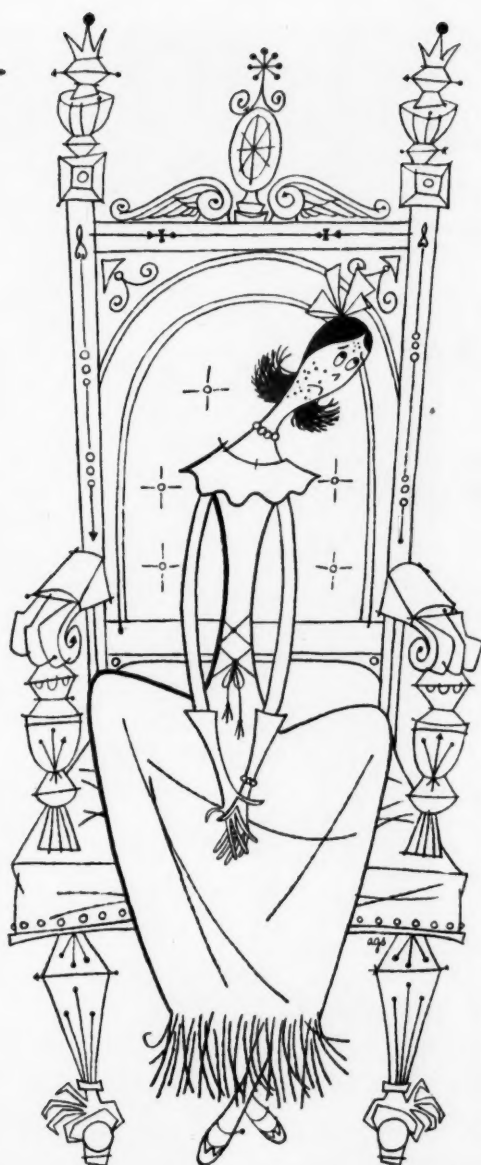
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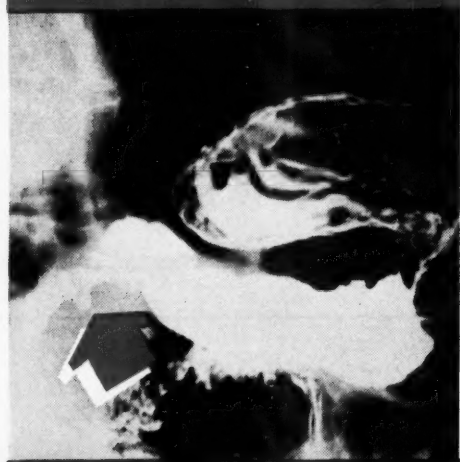
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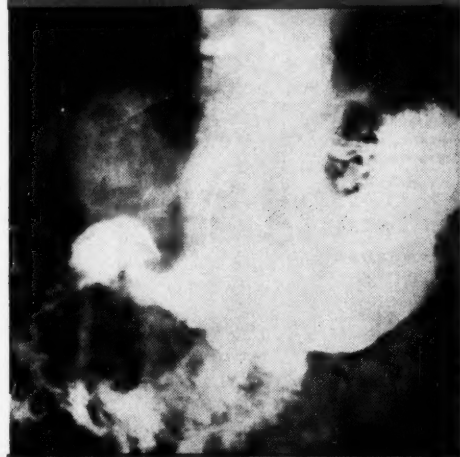
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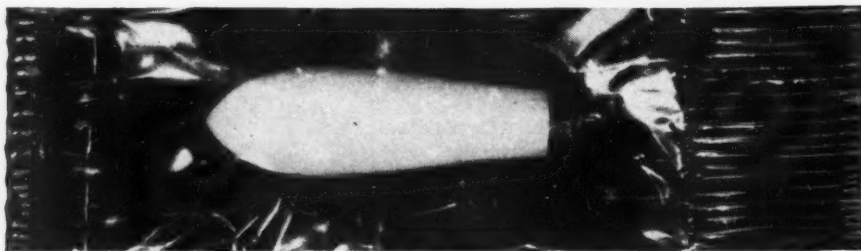
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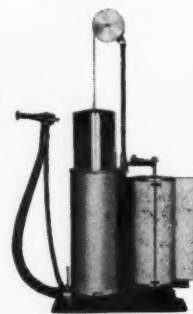
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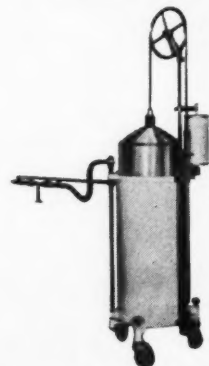
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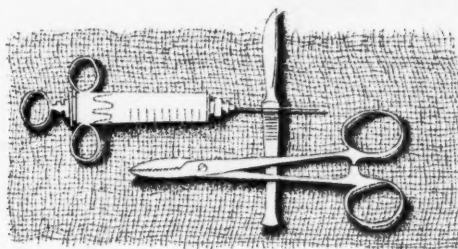


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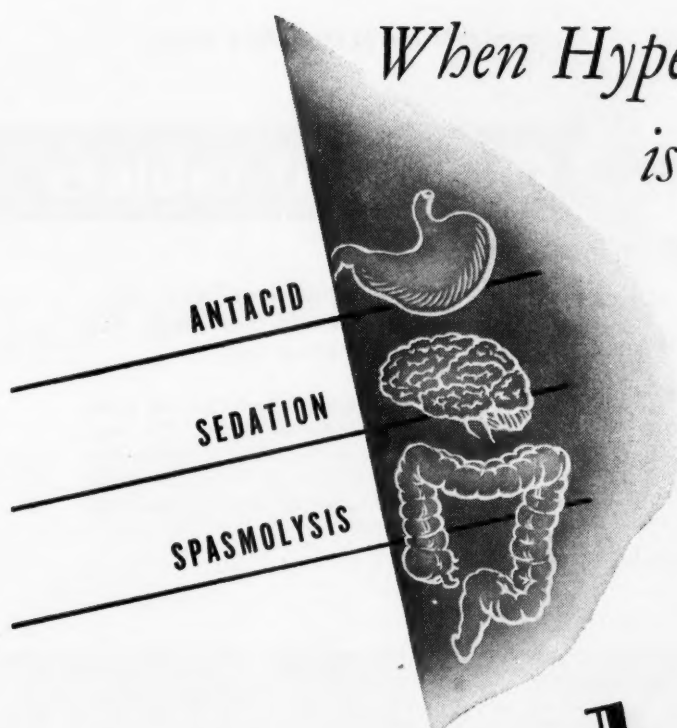
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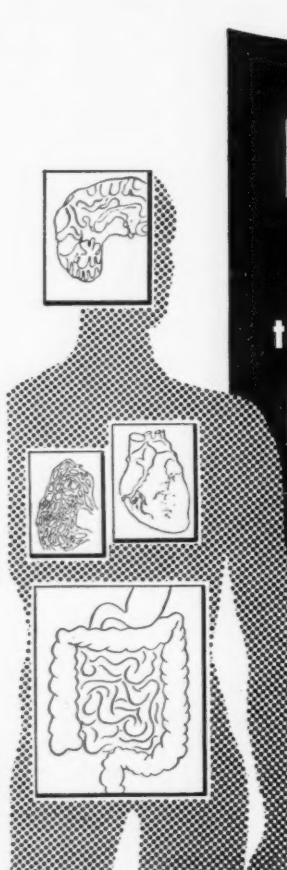
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1. Reeb, B. B., Rohr, J. R., and Colwell, A. R.: *Proc. House Staff Dept. Med., Wesley Memorial Hospital, Chicago, Ill.* Feb. 6, 1948.

2. Rohr, J. H., and Colwell, A. R., *Proc. Amer. Diabetes Assn.* 8:37, 1948.

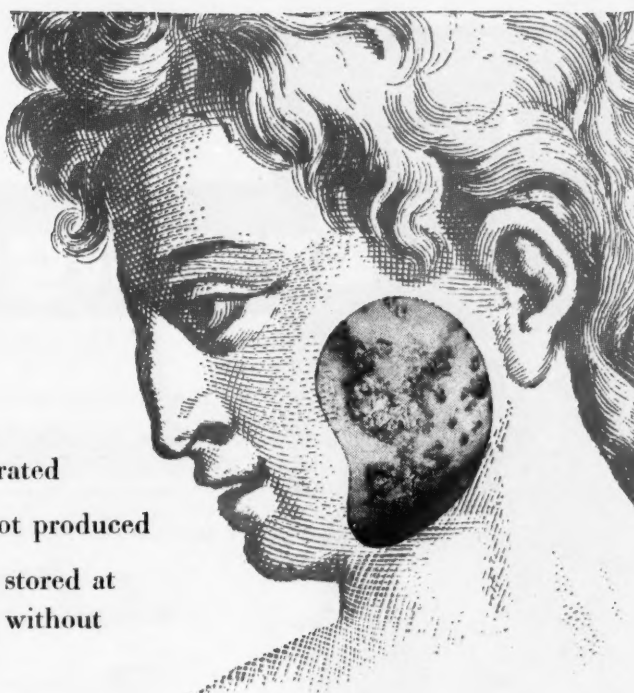
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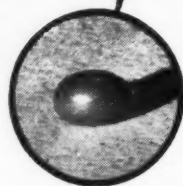
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